

## Original Investigation

# Efficacy of Varenicline Combined With Nicotine Replacement Therapy vs Varenicline Alone for Smoking Cessation

## A Randomized Clinical Trial

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**IMPORTANCE** Behavioral approaches and pharmacotherapy are of proven benefit in assisting smokers to quit, but it is unclear whether combining nicotine replacement therapy (NRT) with varenicline to improve abstinence is effective and safe.

**OBJECTIVE** To evaluate the efficacy and safety of combining varenicline and a nicotine patch vs varenicline alone in smoking cessation.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, blinded, placebo-controlled clinical trial with a 12-week treatment period and a further 12-week follow-up conducted in 7 centers in South Africa from April 2011 to October 2012. Four hundred forty-six generally healthy smokers were randomized (1:1); 435 were included in the efficacy and safety analyses.

**INTERVENTIONS** Nicotine or placebo patch treatment began 2 weeks before a target quit date (TQD) and continued for a further 12 weeks. Varenicline was begun 1 week prior to TQD, continued for a further 12 weeks, and tapered off during week 13.

**MAIN OUTCOMES AND MEASURES** Tobacco abstinence was established and confirmed by exhaled carbon monoxide measurements at TQD and at intervals thereafter up to 24 weeks. The primary end point was the 4-week exhaled carbon monoxide–confirmed continuous abstinence rate for weeks 9 through 12 of treatment, ie, the proportion of participants able to maintain complete abstinence from smoking for the last 4 weeks of treatment, as assessed using multiple imputation analysis. Secondary end points included point prevalence abstinence at 6 months, continuous abstinence rate from weeks 9 through 24, and adverse events. Multiple imputation also was used to address loss to follow-up.

**RESULTS** The combination treatment was associated with a higher continuous abstinence rate at 12 weeks (55.4% vs 40.9%; odds ratio [OR], 1.85; 95% CI, 1.19-2.89;  $P = .007$ ) and 24 weeks (49.0% vs 32.6%; OR, 1.98; 95% CI, 1.25-3.14;  $P = .004$ ) and point prevalence abstinence rate at 6 months (65.1% vs 46.7%; OR, 2.13; 95% CI, 1.32-3.43;  $P = .002$ ). In the combination treatment group, there was a numerically greater incidence of nausea, sleep disturbance, skin reactions, constipation, and depression, with only skin reactions reaching statistical significance (14.4% vs 7.8%;  $P = .03$ ); the varenicline-alone group experienced more abnormal dreams and headaches.

**CONCLUSIONS AND RELEVANCE** Varenicline in combination with NRT was more effective than varenicline alone at achieving tobacco abstinence at 12 weeks (end of treatment) and at 6 months. Further studies are needed to assess long-term efficacy and safety.

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**T**obacco use is the foremost preventable cause of morbidity and mortality from respiratory and cardiovascular diseases and cancer.<sup>1,2</sup> Encouraging smoking cessation and supporting smokers who want to quit should be a priority for all health care professionals. The combination of behavioral approaches and pharmacotherapy are of proven benefit in assisting smokers to quit.<sup>3-7</sup>

The pharmacologic effects of nicotine are mediated via nicotinic receptors on the surface of cells throughout the body, and addiction results from the development of tolerance and mechanisms that reinforce dependence.<sup>7</sup> The nicotinic cholinergic receptor, and specifically the  $\alpha_4\beta_2$  receptor subtype, is believed to be the principal mediator of nicotine dependence.<sup>7</sup> Varenicline targets this receptor with higher affinity than nicotine, blocking nicotine effects but also acting as a partial agonist.<sup>8,9</sup> Nicotine from nicotine replacement therapy (NRT) acts on this cholinergic receptor (as well as other receptor subtypes, including  $\alpha_3\beta_4$ ) in a similar way to nicotine from tobacco smoke, although the pharmacokinetic delivery is significantly slower.<sup>9</sup> As a partial agonist, varenicline may in theory block the direct agonist effects of nicotine, leading to complex pharmacodynamics.<sup>3</sup>

Previous studies have evaluated combining varenicline and NRT as a potential means for increasing abstinence rates. An observational study found no differences in outcome between a cohort of participants receiving various NRT products and varenicline,<sup>10</sup> and a randomized controlled trial suggested that the efficacy of varenicline was not enhanced by the addition of nicotine patches.<sup>9</sup> Both studies found the combination to be safe and well tolerated.<sup>9,10</sup>

The aim of this study was to evaluate the efficacy of combining varenicline and a nicotine patch vs varenicline alone as an aid to smoking cessation in a double-blind study design in a larger group and with a longer assessment period than has been studied to date. The primary end point was the 4-week continuous abstinence rate during weeks 9 through 12 of varenicline treatment.

## Methods

A randomized, double-blind trial was conducted at 7 centers (in Cape Town, Johannesburg, and Durban) in South Africa from April 2011 to October 2012. Participants were randomized to receive varenicline plus placebo patch or varenicline plus nicotine patch. Patches were commenced 2 weeks before a target quit date (TQD) and continued for a further 12 weeks. Varenicline was up-titrated 1 week before the TQD, continued for a further 12 weeks, and tapered off during week 13. Smoking status was established at the TQD and at 1, 2, 4, 8, 12, 16, and 24 weeks thereafter. Written informed consent was obtained from all participants prior to enrollment. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines on Good Clinical Practice, and the protocol was approved by the South African Medicines Control Council, the human research ethics committee of Stellenbosch University, and the independent review board of each center.

## Participant Selection and Randomization

Participants aged 18 to 75 years who sought assistance with smoking cessation, had smoked at least 10 cigarettes/d during the previous year and the month prior to screening, and had had no period of smoking abstinence longer than 3 months in the past year were eligible for the study. No financial incentives were provided. Women of child-bearing potential were allowed to enroll provided they agreed to avoid pregnancy through 30 days after the last dose of study medication, had a negative test for pregnancy (urinary  $\beta$ -human chorionic gonadotropin), and agreed to use an effective birth control method. Participants had to be prepared to attend clinic visits. Only 1 participant per household was allowed. Exclusion criteria are summarized in the **Box**.

Eligible participants were randomized at a second visit (2 weeks before the TQD) into 1 of the 2 groups of the study in a 1:1 ratio using centrally generated block randomization within each site (blocks of 4 with 2 active and 2 placebo patches). Both the investigators and the participants were blinded.

### Box. Exclusion Criteria

- Past or present depression or treatment with antidepressants within the past 12 months
- History of or currently experiencing psychosis, panic disorder, or bipolar disorder
- Severe chronic obstructive pulmonary disease
- Clinically significant cardiovascular disease in the past 6 months, eg, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, unstable angina, serious arrhythmia, and clinically significant conduction abnormalities
- Uncontrolled hypertension or a systolic blood pressure greater than 150 mm Hg or diastolic pressure greater than 95 mm Hg at screening
- Clinically significant neurological disorders or cerebrovascular diseases (eg, stroke, transient ischemic attack, etc) in the past 6 months
- History of clinically significant endocrine disorders or gastrointestinal diseases, including insulin-dependent diabetes mellitus, uncontrolled hyperthyroidism, and active peptic ulcer
- Significant hepatic or renal impairment or other clinically significant abnormal laboratory test values (performed at the discretion of the investigator)
- History of cancer (cured basal cell or squamous cell carcinoma of the skin allowed)
- History of clinically significant allergic reactions to drugs (eg, severe cutaneous and systemic allergic reactions)
- History of drug or alcohol abuse or dependence within the past 12 months
- A body mass index less than 15 or greater than 38 or a weight less than 45.5 kg
- Previous enrollment in a study that included varenicline
- Use of nicotine replacement therapy within the last 6 months
- Use of other investigational drugs within 30 days or 5 half-lives (whichever is longer) before the baseline visit or within 30 days of study completion
- Use of prohibited medications: any antidepressants, including bupropion; antipsychotic agents; mood stabilizers; naltrexone; steroids (inhaled and topical steroids were permitted); or insulin

### Study Procedures and Assessment

Participants completed the Fagerström Test for Nicotine Dependence on enrollment.<sup>11</sup> Further assessment included a medical and smoking history (past attempts to quit smoking and lifetime cigarette use) and a physical examination. Participants were followed up weekly from randomization until the TQD (2 weeks later) and subsequently at 1, 2, 4, 8, and 12 weeks during the treatment period. Follow-up visits were conducted at weeks 13 (telephonic), 16, and 24 during the non-treatment period. Participants were asked at each clinic visit to complete a Nicotine Use Inventory (NUI) to assess continuous abstinence by reporting the use of cigarettes and other nicotine-containing products (other than that provided) since the last contact and, to determine point prevalence, during the preceding 7 days (eMethods 1 in the Supplement).<sup>6</sup> Exhaled carbon monoxide was measured at each visit using a Micro IV Smokerlyzer (Bedfont Scientific). Withdrawal symptoms including tobacco craving were assessed by means of the Wisconsin Scale for Withdrawal Symptoms (eMethods 2 in the Supplement) at randomization and up to 4 weeks after the TQD.<sup>12</sup> Each subscale ranges from 0 (no symptoms) to 4 (severe). Ten minutes of smoking cessation counseling, based on the 2008 update of the US Public Health Service guidelines, was provided to all participants at each visit.<sup>13</sup>

### Study Medication

Active 15-mg nicotine patches (Nicorette, McNeil) or placebo patches were administered for 16 h/d beginning at the randomization visit, 2 weeks before the TQD, and continued until week 12 (total duration, 14 weeks). Placebo patches were supplied by the same manufacturer and were similar in appearance (and packaging) to active patches. One week before the TQD, all participants began taking varenicline (Pfizer), 0.5 mg once daily for 3 days, titrated to 0.5 mg twice daily for days 4 to 7 and then to the maintenance dose of 1 mg twice daily through week 12. Varenicline was tapered off and stopped at the end of week 13 (0.5 mg twice daily for 4 days, followed by 0.5 mg in the evenings for 3 days; total duration, 14 weeks).

### Outcome Measures

The efficacy analysis population consisted of participants who took at least 1 dose of varenicline while using the randomized nicotine patch. The primary end point was the 4-week continuous abstinence rate for weeks 9 through 12 of varenicline treatment, ie, the proportion of participants who were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 4 weeks of treatment, confirmed with end-expiratory exhaled carbon monoxide measurements of 10 ppm or less at week 12.

Secondary end points included the point prevalence abstinence at 6 months, the continuous abstinence rate from week 9 through 24, and the incidence of adverse events. Participants who answered yes to any of the NUI questions pertaining to the preceding 7 days or who had an exhaled carbon monoxide measurement greater than 10 ppm were all considered to be smokers in the calculation of point prevalence abstinence, whereas participants who answered yes to any of the NUI questions or who had an exhaled carbon monoxide mea-

surement greater than 10 ppm at weeks 12, 16, and 24 were all considered not to have achieved continuous abstinence at 6 months.

Participants who discontinued the study or were lost to follow-up were considered smokers in the per-protocol and intention-to-treat calculations of continuous abstinence rates of both the primary and secondary end points. Participants who missed a visit were considered to be smokers at that point in the per-protocol analysis.

All adverse events were recorded at each visit after randomization, and all participants who were followed up at least once after the initiation of any study medication were included in the safety analysis.

### Statistical Aspects

The efficacy of varenicline to achieve the primary outcome of continuous abstinence in weeks 9 through 12 was estimated to be 45%, and our initial assumption was that a 12% further increase in the 4-week abstinence rate in the NRT active group would represent a clinically relevant treatment outcome difference.<sup>4-6</sup> However, a subsequent study combining varenicline with a nicotine gum reported a 16% additional increase in abstinence.<sup>14</sup> Accordingly, we increased our required value for clinical relevance to 14%. Using this value, at a 5% significance level and 80% power (2-tailed,  $\alpha = .05$ ), the sample size was calculated at 199 per group (total sample size of 398). Assuming the attrition rate at the end of treatment would not exceed 10%, we required a further 40 participants, resulting in an estimated sample size of 438 participants.

Descriptive statistics and  $\chi^2$  or Fisher exact tests were performed on dichotomous categorical variables, and *t* tests on continuous data in both the per-protocol and intention-to-treat analyses (which included all randomized participants). A logistic regression model was fitted to the primary binary end point and included treatment center as an independent variable. Analyses were conducted using SPSS software (version 21; IBM). A post hoc multiple imputation analysis was performed to account for missing data using Stata software (version 13; StataCorp). A logit model was used to impute the outcome for participants who did not attend their 12- and 24-week follow-up visits, based on the parameters of age, sex, body mass index, Fagerström test score, years smoked, daily average cigarettes smoked, pack-years smoked, previous attempts to quit, and treatment group. Five imputations were performed. Bivariable logistic models were then fitted with the imputed values using treatment group as the predictor variable for comparison with the per-protocol analysis. An additional post hoc logistic mixed model analysis was also performed (eMethods 3 in the Supplement).

## Results

A total of 446 participants (171 males; mean [SD] age, 46.3 [11.9] years) were enrolled and randomized (Figure). Of these, 435 were included in the per-protocol efficacy and safety analyses. Demographic characteristics and smoking history of the participants are summarized in Table 1.

Figure. Participant Flow Through the Study

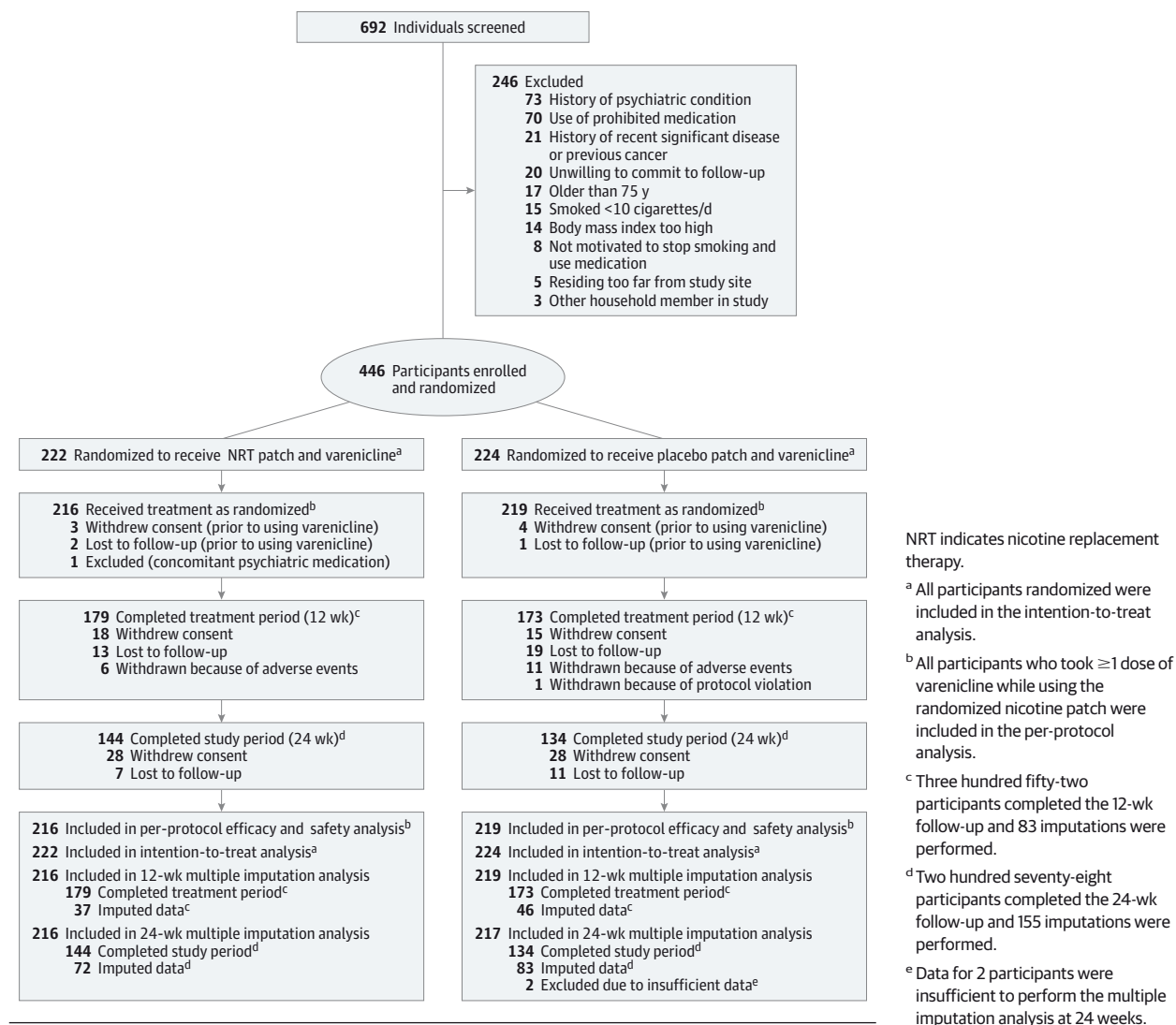


Table 1. Baseline Characteristics of All Participants Randomized (N=446)

Characteristic	Mean (SD)	
	Varenicline and Active Nicotine Patch (n = 222)	Varenicline and Placebo Patch (n = 224)
Age, mean (SD), y	46.6 (11.9)	46.1 (11.9)
Male, No. (%)	87 (39.2)	84 (37.5)
Body mass index <sup>a</sup>	27.1 (4.8)	27.5 (5.5)
Fagerström score <sup>b</sup>	4.5 (1.3)	4.5 (1.4)
Smoking history		
Years smoked	26.8 (11.2)	26.0 (11.8)
Cigarettes, No./d	15.5 (6.8)	16.1 (6.9)
Pack-years	21.3 (14.8)	21.4 (14.1)
Previous quit attempts, mean (range), No.	1.55 (0-11)	1.37 (0-15)

<sup>a</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup> The Fagerström score for nicotine dependence ranges from 0 to 10; a higher score denotes greater dependency.

**Abstinence Rates and Craving for Cigarette Smoking**

The continuous and the point prevalence abstinence rates for the per-protocol and multiple imputation analyses are presented in Table 2. Participants who received active NRT and varenicline were more likely to achieve continuous abstinence at 12 weeks (55.4% vs 40.9%;  $P = .007$ ) and 24 weeks (49.0% vs 32.6%;  $P = .004$ ) and point prevalence abstinence at 24 weeks (65.1% vs 46.7%;  $P = .002$ ) than those receiving placebo NRT and varenicline. The differences observed in continuous abstinence were 14.5% (95% CI, 5.2%-23.8%) at 12 weeks and 16.4% (95% CI, 7.2%-25.5%) at 24 weeks, and the numbers needed to treat (NNT) to achieve 1 additional successful attempt at smoking cessation were 7 (95% CI, 5-20) and 7 (95% CI, 4-14), respectively. The difference observed in point prevalence abstinence at 24 weeks was 18.4% (95% CI, 9.5%-27.9%) and the NNT, 6 (95% CI, 4-11).

Results of the intention-to-treat analysis of the primary end point provided similar results. Continuous abstinence at 12 weeks was observed in 99 of 222 participants (44.6%;

Table 2. Continuous Abstinence and Point Prevalence Abstinence Rates (n=435)

Time Since TQD	Time Period	Per-Protocol Analysis				Multiple Imputation Analysis of Main Outcomes			
		No. (%)		OR (95% CI)	P Value	No. (%) <sup>a</sup>		OR (95% CI)	P Value
		Varenicline and Active Nicotine Patch (n = 216)	Varenicline and Placebo Patch (n = 219)			Varenicline and Active Nicotine Patch (n = 216)	Varenicline and Placebo Patch <sup>b</sup>		
<b>Continuous Abstinence</b>									
8 wk	Weeks 5-8	96 (44.4)	76 (34.7)	1.50 (1.02-2.22)	.04				
12 wk	Weeks 9-12	99 (45.8)	70 (32.0)	1.80 (1.22-2.66)	.003	120 (55.4)	90 (40.9)	1.85 (1.19-2.89)	.007
16 wk	Weeks 9-16	84 (38.9)	56 (25.6)	1.85 (1.23-2.79)	.003				
24 wk	Weeks 9-24	71 (32.9)	42 (19.2)	2.06 (1.33-3.21)	.001	106 (49.0)	71 (32.6)	1.98 (1.25-3.14)	.004
<b>Point Prevalence Abstinence Rates</b>									
1 wk	Week 1	69 (31.9)	61 (27.9)	1.22 (0.81-1.83)	.35				
2 wk	Week 2	98 (45.4)	95 (43.4)	1.08 (0.74-1.58)	.68				
4 wk	Week 4	110 (50.9)	87 (39.7)	1.57 (1.08-2.30)	.02				
8 wk	Week 8	109 (50.5)	96 (43.8)	1.31 (0.90-1.90)	.17				
12 wk	Week 12	116 (53.7)	87 (39.7)	1.76 (1.20-2.58)	.003	138 (63.9)	112 (51.2)	1.68 (1.07-2.66)	.03
16 wk	Week 16	104 (48.1)	81 (37.0)	1.58 (1.08-2.32)	.02				
24 wk	Week 24	94 (43.5)	63 (28.8)	1.91 (1.28-2.84)	.001	141 (65.1)	101 (46.7)	2.13 (1.32-3.43)	.002

Abbreviations: OR, odds ratio; TQD, target quit date.

<sup>a</sup> Calculated mean proportional values (numbers rounded) derived from data of participants who completed follow-up to 12 and 24 weeks, respectively, and, to account for missing data, 5 sets of imputed values for the participants who

did not attend their 12- and 24-week follow-up visits (Figure). Data for 2 participants (in the placebo group) were insufficient to perform the multiple imputation analysis at 24 weeks.

<sup>b</sup> n = 219 at 12 wk and n = 217 at 24 wk.

Table 3. Adverse Events Reported in at Least 2% of Participants per Study Group

Adverse Event	No. (%)		P Value
	Varenicline and Active Nicotine Patch (n = 216)	Varenicline and Placebo Patch (n = 219)	
Nausea	59 (27.3)	54 (24.7)	.53
Insomnia and disturbed sleep	43 (19.9)	35 (15.1)	.18
Abnormal dreams	10 (4.6)	13 (5.9)	.54
Headaches	17 (7.9)	22 (10.0)	.43
Any skin reactions	31 (14.4)	17 (7.8)	.03
Constipation	9 (4.1)	6 (2.7)	.42
Depression	5 (2.3)	3 (1.4)	.50 <sup>a</sup>

<sup>a</sup> Fisher exact probability test (all other P values were calculated with  $\chi^2$  test).

95% CI, 38.0%-51.4%) vs 70 of 224 participants (31.3%; 95% CI, 25.3%-37.8%) randomized to receive the addition of NRT vs placebo, respectively (OR, 1.77; 95% CI, 1.18-2.66;  $P = .004$ ).

When considering site as a clustering variable and modeling the effect with clustering by site adjusted for using robust standard errors, logistic regression analysis showed that for the main outcome of continued abstinence (weeks 9-12), no change in the effect was observed, and the differences remained significant (OR, 1.80; 95% CI, 1.30-2.50;  $P < .001$ ). The post hoc logistic mixed model analysis also confirmed significant differences in rate of abstinence over time between the 2 groups (eResults in the Supplement).

The craving for cigarette smoking, as measured by the Wisconsin Scale for Withdrawal Symptoms (range, 0-4), did not differ between the active and placebo NRT groups at random-

ization (2.59; 95% CI, 2.48-2.70 vs 2.66; 95% CI, 2.55-2.78;  $P = .41$ ); nor did it differ at the TQD (2.20; 95% CI, 2.08-2.32 vs 2.32; 95% CI, 2.20-2.43;  $P = .19$ ) or at 4 weeks after the TQD (1.73; 95% CI, 1.52-1.95 vs 1.63; 95% CI, 1.43-1.84;  $P = .51$ ) among participants who abstained from smoking during the preceding 7 days. No significant differences in the other variables of the scale were observed.

### Safety, Tolerability, and Compliance

The mean weight gain in those who completed 6 months of follow-up was 3.0 kg (95% CI, 2.3-3.8 kg) in the active and 2.2 kg (95% CI, 1.7-2.8 kg) in the placebo NRT groups, respectively ( $P = .09$ ). Other adverse events that were observed at any time during the treatment phase or follow-up are summarized in Table 3. Skin reactions reported in the active NRT patch group included localized erythema (n = 21) or

itch ( $n = 6$ ), whereas 3 patients experienced mild generalized reactions and a single participant reported worsening of preexisting acne. Cutaneous adverse events in the placebo NRT patch group included localized erythema ( $n = 11$ ) or itch ( $n = 2$ ), mild generalized dermatitis ( $n = 3$ ), and gingivitis ( $n = 1$ ).

Two women became pregnant during the treatment phase (both were randomized to receive the placebo NRT patch). One pregnancy was anembryonic and considered an unrelated serious adverse event (SAE). Another participant gave birth to an infant with Down syndrome (confirmed trisomy 21) with associated congenital heart defects. There was no family history of chromosomal abnormalities, and it was considered a possibly related SAE. Five other unrelated SAEs were reported during follow-up: 4 among participants randomized to receive the active patch and 1 to receive the placebo patch.

Overall, 140 (78.2%) and 137 (76.5%) participants randomized to receive the NRT patch and who completed the treatment period (12 weeks) showed at least an 80% adherence with varenicline and the patch, respectively, compared with 139 (80.3%) and 143 (82.7%) participants randomized to receive the placebo patch.

## Discussion

In this study, to our knowledge the largest study to date examining the efficacy and safety of supplementing varenicline treatment with NRT, we have found the combination treatment to be associated with a statistically significant and clinically important higher continuous abstinence rate at 12 and 24 weeks, as well as a higher point prevalence abstinence rate at 6 months.

A recent Cochrane analysis covering 267 studies confirmed that varenicline was more effective than nicotine patch (OR, 1.51; 95% CI, 1.22-1.87), nicotine gum (OR, 1.72; 95% CI, 1.38-2.13), and other NRT (OR, 1.42; 95% CI, 1.12-1.79), but not more effective than a combination of NRT formulations (OR, 1.06; 95% CI, 0.75-1.48) in increasing the odds of quitting.<sup>15</sup> Of note, combination NRT also outperformed single-formulation NRT.<sup>15</sup> In a recent study, Ebbert et al<sup>16</sup> reported that the combined use of varenicline and bupropion, compared with varenicline alone, did not increase the point prevalence abstinence at 26 weeks (38.2% vs 31.9%,  $P = .14$ ).<sup>16</sup>

To date, only a single double-blind randomized controlled trial has compared varenicline with the combination of varenicline and NRT patch.<sup>9</sup> Hajek et al<sup>9</sup> found that the combination treatment did not improve biochemically validated abstinence rates at 1 and 4 weeks after the TQD compared with varenicline and placebo patch (69% vs 59%,  $P = .28$ , and 60% vs 59%,  $P = .91$ ) or self-reported abstinence rates at 12 weeks (36% vs 29%;  $P = .39$ ). The authors acknowledged that their study may have been inadequately powered to reject the null hypothesis (no benefit in the combination), given the relatively small sample size ( $n = 117$ ) and short follow-up (12 weeks). Moreover, abstinence at 12 weeks was self-reported (not bio-

chemically validated), and up to 5 lapses were permitted. The present study's larger sample size, longer duration of follow-up, and the use of a rigorous definition of abstinence (including regular monitoring of nicotine use and exhaled carbon monoxide) may account for the different results. Other strengths of our study are its blinded design and multiple-center components, which may have increased heterogeneity among participants.

The additive efficacy of combining the 2 drugs is not easily explained, given that both target  $\alpha_4\beta_2$  nicotine receptors.<sup>7</sup> It is possible that neither varenicline nor nicotine fully saturate all  $\alpha_4\beta_2$  nicotine receptors in the brain, leaving room for the action of the other. Alternatively, nicotine replacement may bind to different (additional) receptors involved in nicotine dependency. Interestingly, we found no evidence that combination therapy decreased craving for nicotine. A further possibility is that the different pharmacokinetics of the 2 components provide a more favorable onset of receptor agonism. The onset of action of nicotine released from NRT, for example, is slower than that of nicotine from smoking or that of varenicline.<sup>3</sup> Finally, it is possible that the phased introduction of varenicline 1 week after NRT or tapering of varenicline might in some way have improved the effectiveness of the combination. Had the pretreatment with NRT been responsible for the superior abstinence rate, this would have been expected to wane over time. The opposite was observed. There is currently also no evidence that quit rates are higher with gradual reduction in smoking compared with abrupt quitting.<sup>17,18</sup>

The present study was not adequately powered to assess safety and tolerability end points. In the combination group, there was a numerically greater incidence of nausea, sleep disturbance, skin reactions, constipation, and depression, with only skin reactions reaching statistical significance (14.4% vs 7.8%,  $P = .03$ ); participants in the varenicline-alone group reported more abnormal dreams and headaches. The incidence of skin reactions was comparable with reported figures for NRT patches.<sup>19</sup> Hajek et al<sup>9</sup> also reported a favorable safety profile, with only vivid dreams being reported more frequently in the combination group (20.7% vs 8.5%,  $P = .06$ ). The birth of an infant with Down syndrome (trisomy 21) in a participant randomized to receive the placebo patch was reported as possibly drug related owing to the category C status of varenicline and the temporal relationship to treatment. However, causality seems unlikely given the mechanism of action of the drug and the absence to date in postmarketing research of this association.<sup>20,21</sup>

Our study had potential limitations. Only 62.3% of randomized participants completed the study. Moreover, 11 randomized participants (2.5%) did not take 1 dose of varenicline and were excluded from the per-protocol analyses. The high attrition rate may be a reason for the relatively modest per-protocol abstinence rates when compared with earlier reported figures<sup>5</sup> but does not account for the differences observed, as our post hoc multiple imputation analysis confirmed that the missing outcomes did not bias the per-protocol efficacy analysis. We limited our study population to relatively healthy smokers because the potential for unexpected ad-

verse events was unknown. These aspects, as well as the specific timing of initiation of both interventions and the tapering of varenicline, may differ from the everyday practice and limit the generalizability of our findings. Future studies should include a broader range of smokers, other forms of NRT, and more detailed assessments of tolerability and cost/benefit comparisons with alternative therapies.

## Conclusions

Varenicline in combination with NRT was more effective than varenicline alone at achieving smoking abstinence at 12 weeks and 6 months. Further studies are needed to assess long-term efficacy and safety.

### ARTICLE INFORMATION

**Author Contributions:** Dr Koegelenberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Koegelenberg, Noor, Irusen.

**Acquisition, analysis, or interpretation of data:** Koegelenberg, Noor, Bateman, van Zyl-Smit, Bruning, O'Brien, Smith, Abdool-Gaffar, Emanuel, Esterhuizen, Irusen.

**Drafting of the manuscript:** Koegelenberg, Noor, Bateman, Irusen.

**Critical revision of the manuscript for important intellectual content:** van Zyl-Smit, Bruning, O'Brien, Smith, Abdool-Gaffar, Emanuel, Esterhuizen.

**Statistical analysis:** Koegelenberg, Noor, Esterhuizen.

**Obtained funding:** Noor.

**Administrative, technical, or material support:** Koegelenberg, Noor, Bateman, van Zyl-Smit, O'Brien, Smith, Abdool-Gaffar, Irusen.

**Study supervision:** Noor, Irusen.

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