Article

# Combination Treatment With Varenicline and Bupropion in an Adaptive Smoking Cessation Paradigm

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**Objective:** The authors assessed the efficacy and safety of combination treatment with varenicline and sustained-release bupropion for smokers who, based on an assessment of initial smoking reduction prior to the quit date, were deemed unlikely to achieve abstinence using nicotine patch treatment.

**Method:** In a randomized, double-blind, parallel-group adaptive treatment trial, the authors identified 222 cigarette smokers who failed to show a reduction of more than 50% in smoking after 1 week of nicotine patch treatment. Smokers were randomly assigned to receive 12 weeks of varenicline plus bupropion or varenicline plus placebo. The primary outcome measure was continuous smoking abstinence at weeks 8–11 after the target quit date.

**Results:** Both treatments were well tolerated. Participants who received the combination treatment had a significantly higher abstinence rate than those who received varenicline plus placebo (39.8% compared with 25.9%; odds ratio=1.89; 95% CI=1.07, 3.35). Combination treatment had a significantly greater effect on abstinence rate in male smokers (odds ratio=4.26; 95% CI=1.73, 10.49) than in female smokers (odds ratio=0.94; 95% CI=0.43, 2.05). It also had a significantly greater effect in highly nicotine-dependent smokers (odds ratio=3.51, 95% CI=1.64, 7.51) than in smokers with lower levels of dependence (odds ratio=0.71, 95% CI=0.28, 1.80).

**Conclusions:** Among smokers who did not show a sufficient initial response to prequit nicotine patch treatment, combination treatment with varenicline and bupropion proved more efficacious than varenicline alone for male smokers and for smokers with a high degree of nicotine dependence.

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Cigarette smoking is a leading cause of premature death and disease in the United States and in developing countries throughout the world (1). According to recent studies, smoking is even more lethal than previously believed, with continuing smokers experiencing nearly three times the death rate of nonsmokers (2). Smoking cessation demonstrably reduces the risk of smoking-related mortality, and the younger a smoker is when he or she quits, the greater the benefit of quitting (3). Unfortunately, with current pharmacotherapies, which include nicotine replacement therapy, varenicline, and sustained-release bupropion, success rates remain low, with less than 25% of smokers remaining abstinent 1 year after treatment (4).

To increase the efficacy of smoking cessation treatment, we have developed and validated an adaptive treatment approach designed to provide each smoker with the treatment most likely to succeed, while minimizing risks and side effects. According to this strategy, smokers initially receive nicotine patch treatment starting 2 weeks before a target quit date. The initiation of nicotine replacement therapy before the quit date has been shown to be well tolerated, and several studies have found it to enhance continuous smoking abstinence (5–7). Moreover, it allows the early identification of positive responders to nicotine replacement, based on the extent to which ad lib smoking declines in the first week of prequit nicotine patch treatment. We found in previous studies (8, 9) that smokers who did not decrease their smoking by more than 50% in the first week had a much lower abstinence rate after the quit date than smokers who reduced their smoking by more than 50%. Using this early marker of nicotine patch response to guide subsequent treatment, we were able to prevent approximately 10% of treatment failures among patch nonresponders by modifying the treatment before the target quit date, either by switching to varenicline or augmenting nicotine replacement therapy with bupropion (9).

Given that varenicline and bupropion have different mechanisms of action, it is reasonable to hypothesize that their therapeutic effects might be additive. This rationale was supported by recent open-label investigations suggesting that combination treatment with varenicline and bupropion was well tolerated and potentially highly efficacious (10, 11). Inasmuch as combination treatment with two drugs that carry FDA black box warnings may face

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significant hurdles in becoming a first-line therapy, a more feasible approach may be to evaluate the usefulness of this combination treatment for smokers who are not likely to succeed in quitting with nicotine patch treatment alone. In the present study, we evaluated whether combination treatment with varenicline and bupropion is more efficacious than varenicline alone as a rescue treatment for nicotine patch nonresponders.

## Method

### Study Design

The study was a double-blind, parallel-arm adaptive treatment trial, in which early response to nicotine patch treatment was assessed in a prequit phase, after which nicotine patch nonresponders who failed to show a decrease of >50% in ad lib smoking (assessed using expired-air CO) were randomly assigned to receive either varenicline plus bupropion (N=113) or varenicline plus placebo (N=109). (The nicotine patch prequit responders were entered into a separate study to explore combination nicotine replacement therapy treatment, the results of which will be reported elsewhere.)

### Study Procedures

The study was approved by the Duke University Medical Center Institutional Review Board. Adult smokers expressing a desire to quit smoking were recruited through newspaper, radio, and television advertisements. To be eligible, participants had to be 18–65 years of age, report smoking an average of ≥10 cigarettes per day for 3 cumulative years, have an expired-air CO level ≥10 ppm, and have no exclusionary features on history, physical examination, or laboratory evaluation (see the data supplement that accompanies the online edition of this article). Participants provided written informed consent after receiving a complete description of the study, and they were compensated up to $330 for study participation.

After screening and enrollment in the study, participants were seen at our research center weekly for 2 weeks before the quit date and at four sessions held 1, 3, 7, and 11 weeks after the quit date. Brief support (<15 minutes) was provided at each session, and clinical trial materials were dispensed. Smoking diaries and measures of expired-air CO were collected at each session.

After the first week of prequit nicotine patch treatment, all patch nonresponders were randomly assigned to receive varenicline along with either sustained-release bupropion tablets or placebo tablets that were identical in appearance. The recommended dosing titration schedule was used for both varenicline (0.5 mg once daily on days 1–3; 0.5 mg twice daily on days 4–7; and 1 mg twice daily through 12 weeks) and bupropion (150 mg daily for 3 days, then 150 mg twice daily through 12 weeks).

Initial nicotine patch dosing was based on initial expired-air CO reading; participants with CO levels >30 ppm at baseline received 42 mg/day (two 21-mg/day patches), and the remaining participants received a single 21 mg/day patch. In the 21 mg/day condition, one 21-mg patch was applied each morning; in the 42 mg/day condition, a 21-mg patch was applied each morning and a second patch at noon (which has been found to reduce the likelihood of nausea). This personalized dosing regimen was based on previous research suggesting that heavy smokers may not receive adequate nicotine replacement with a 21-mg patch (12, 13).

Dosage reductions for medications were allowed in the event of adverse effects. Adverse effect ratings were collected using 7-point rating scales.

### Statistical Analysis

Treatment groups were initially compared on demographic and smoking history variables, using analysis of variance, to identify potential confounding factors.

To evaluate the hypothesis that combination treatment with varenicline and bupropion would enhance abstinence rates compared with varenicline alone, logistic regression was used to compare the two treatment groups on the primary outcome of continuous abstinence at end of treatment (weeks 8–11 after the target quit date). Abstinence was identified by self-report of no smoking confirmed by expired-air CO levels ≤10 ppm. A secondary outcome measure was point (7-day) abstinence at 6 months (self-reported abstinence confirmed by expired-air CO level at the follow-up).

In an intent-to-treat analysis, participants who withdrew from the study or were lost to follow-up were classified as nonabstinent, consistent with previous reports suggesting that dropouts are very likely to be smoking (14). However, if not all dropouts are smoking, then this failure imputation for study dropouts might lead to reduced estimates of variance, biased conclusions, or elevated rates of type I error (15). Similar problems occur with standard imputation methods that erroneously assume that data are missing at random with respect to treatment outcome. In our sample, a high proportion of dropouts reported at the session immediately preceding withdrawal that they had been smoking, which suggests that the missing-at-random assumption was tenuous. Accordingly, we estimated two logistic regression models to model the probabilities of dropping out and of smoking based on individual participant characteristics and smoking status at previous time points, carrying the associated coefficients forward into separate imputation models (using PROC MI in SAS, version 9.2 [SAS Institute, Cary, N.C.]). A third set of imputation models was estimated based on procedures described by Hedeker et al. (15), using a variety of assumed odds ratios to model the probability of smoking among study dropouts. Results from these and the latter two imputations were combined into single estimates as described by Schafer (16) (using PROC MIANALYZE). A sensitivity analysis was then conducted to determine how robust the conclusions were to the different assumptions underlying these various imputation regimes (including last observation carried forward and missing=smoking).

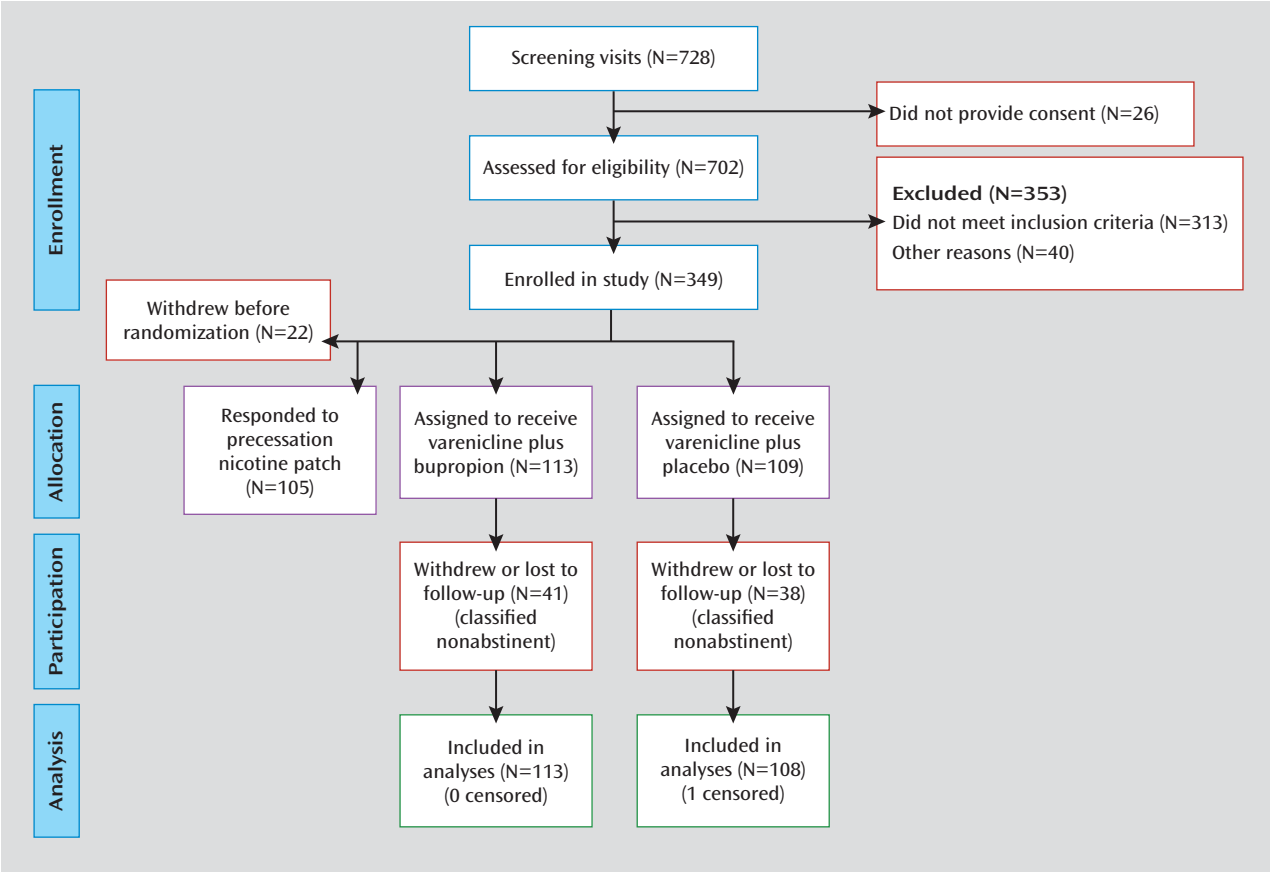
Demographic variables, including sex, were examined for potential moderating effects on treatment outcome. Additionally, we sought to replicate two specific findings reported in a recent article published after the completion of the present study. Ebbert et al. (17) reported that levels of nicotine dependence and cigarette consumption moderated the efficacy of combination treatment with varenicline and bupropion, with more highly dependent smokers (a score >5 on the Fagerström Test for Nicotine Dependence) and heavier smokers (≥20 cigarettes/day) showing a greater therapeutic response to the combination treatment. The same baseline variables (and their interaction with treatment condition) were therefore included in our logistic regression models to assess their potential association with treatment outcome.

Adverse effects were tabulated according to severity and compared between treatments using chi-square tests.

## Results

Of 728 smokers screened, 349 were enrolled in the study and 222 participants who were nicotine patch nonresponders at week 1 were randomly assigned to the two rescue treatment conditions (Figure 1). Of these 222 participants, 221 were included in the analyses; one participant was censored because of a positive pregnancy test reported on the first day of treatment, which was promptly discontinued. In all, 35.6% of participants dropped out after

**FIGURE 1. CONSORT Flow Diagram for a Study of Combination Treatment With Varenicline and Bupropion in an Adaptive Smoking Cessation Paradigm**




randomization. The main reasons cited for discontinuation were scheduling conflict or other personal circumstance (10.4%), loss of interest (5.8%), treatment-related adverse effects (3.2%), and inability to quit smoking (1.4%); 12.2% could not be contacted.

### *Participant Characteristics*

The demographic characteristics and smoking histories of participants were similar across the two treatment conditions (Table 1). Overall, 45.7% were men and 62.4% were white. The participants' mean age was 44.1 years. On average, they smoked 20.7 cigarettes per day and had smoked for 26 years. They had made a mean of 7.2 previous quit attempts, and the mean score on the Fagerström Test for Nicotine Dependence was 6.1, indicating a moderate level of dependence.

### *Efficacy*

In an intent-to-treat analysis that included dropouts as well as study completers, the primary outcome of 4-week smoking abstinence for weeks 8–11 showed a significant effect of combination treatment with varenicline and bupropion (39.8%) relative to varenicline plus placebo (25.9%) (odds ratio=1.89, 95% CI=1.07, 3.35; p=0.029). However, the therapeutic effect of the combination was confined to male smokers (Table 2, Figure 2), for whom the abstinence rate was 50.9% for those receiving the combination treatment and 19.6% for those receiving varenicline plus placebo. In female smokers, there was no significant difference between treatment conditions; abstinence rates were 29.3% for those receiving the combination treatment and 30.6% for those receiving varenicline plus placebo. In a logistic regression model including treatment, sex, and their interaction, the sex-by-treatment interaction was significant (p=0.013).

To determine the extent to which the sex-by-treatment interaction could be accounted for by other baseline demographic and smoking history variables (see Table 1), these variables were examined for sex differences. None were found, with the exception of mean number of previous quit attempts, which was higher for men than for women (9.8 compared with 4.9; F=7.04, df=1, 217, p=0.008). However, this variable did not account for the sex-by-treatment interaction, which remained significant after number of quit attempts was entered as a covariate in the logistic regression model.

Based on findings reported by Ebbert et al. (17), the interactions of treatment with baseline levels of nicotine dependence and cigarette consumption were examined. The dependence-by-treatment interaction was significant (p=0.009), with abstinence increasing in highly dependent smokers but not in smokers with lower levels of dependence (see Table 2, Figure 2). Both of these interactions remained significant when included in the same

**TABLE 1. Baseline Demographic and Smoking Characteristics of Participants in a Study of Combination Treatment With Varenicline and Bupropion**

| Characteristic | Varenicline Plus Placebo (N=108) | | Varenicline Plus Bupropion (N=113) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (years) | 44.5 | 12.6 | 43.7 | 10.5 |
| Years of smoking | 26.9 | 11.5 | 25.2 | 10.3 |
| Number of cigarettes per day | 20.6 | 8.8 | 20.7 | 8.5 |
| Fagerström Test for Nicotine Dependence score | 6.0 | 1.8 | 6.2 | 2.0 |
| Number of previous quit attempts | 6.8 | 12.7 | 7.5 | 14.5 |
| Expired-air CO level (ppm) | 24.8 | 10.8 | 24.6 | 9.6 |
| | N | % | N | % |
| Male | 46 | 42.6 | 55 | 48.7 |
| Race | | | | |
| White | 70 | 64.8 | 68 | 60.2 |
| Black | 32 | 29.6 | 41 | 36.3 |
| Asian | 2 | 1.9 | 0 | 0.0 |
| Other | 4 | 3.7 | 4 | 3.5 |
| Expired-air CO level >30 ppm (treated initially with 42 mg/day nicotine replacement) | 38 | 35.2 | 35 | 31.0 |

logistic regression model (p=0.005 for the sex-by-treatment interaction and p=0.003 for the dependence-by-treatment interaction). Both interactions were also found to be relatively robust when subjected to the above-described sensitivity analysis using multiple imputations for study dropouts (p values ranging from 0.06 to 0.0001).

The interaction of treatment with baseline cigarette consumption was not significant, but the pattern of abstinence rates was nonetheless consistent with the interaction reported by Ebbert et al. (17), inasmuch as the combination treatment was found to be more efficacious than varenicline plus placebo in heavy smokers but not in lighter smokers (see Table 2, Figure 2).

**Six-month follow-up.** Point abstinence at 6 months showed a pattern of findings similar to that of abstinence at the end of treatment, with a significant treatment-by-sex interaction (p=0.06) and a significant treatment-by-baseline nicotine dependence interaction (p=0.006); the interaction of treatment with baseline cigarette consumption was not significant. The combination treatment was more efficacious than varenicline plus placebo in male smokers (29.1% compared with 10.9%; simple effect odds ratio=3.36, 95% CI=1.12, 10.06; p=0.03), and more highly dependent smokers (29.2% compared with 10.0%; simple effect odds ratio=3.71, 95% CI=1.46, 9.41; p=0.006). Among heavier smokers, the abstinence rate at 6 months was higher for those receiving combination treatment than those receiving varenicline alone (25.4% compared with 13.4%), but the association fell short of significance (simple effect odds ratio=2.19, 95% CI=0.90, 5.35; p=0.08). No significant differences were detected for female smokers (22.4% compared with 21.0%; simple effect odds ratio=1.09, 95% CI=0.46, 2.60), lighter smokers (26.1% compared with 22.0%; simple effect odds ratio=1.26, 95% CI=0.47, 3.38), and less dependent smokers (19.5% compared with 28.9%; simple effect odds ratio=0.60, 95% CI=0.21, 1.69).

### *Safety, Tolerability, Adherence, and Weight Gain*

**Adverse events.** A few serious adverse events occurred during the study. One participant in the varenicline-plus-placebo condition (who had also been receiving lisinopril for hypertension) was hospitalized with kidney failure and subsequently discharged; in the varenicline-plus-bupropion condition, one participant was involved in a nonfatal auto collision and another was hospitalized with a methicillin-resistant *Staphylococcus aureus* cellulitis of the leg originating from a bite. None of these adverse events could clearly be attributed to the treatments received.

**Tolerability and adherence to treatments.** Nicotine patches, administered in week 1, were well tolerated overall, with only 0.7% of participants requiring patch dosage reductions in the 21 mg/day condition and 11% in the 42 mg/day condition ($\chi^2$=13.33, df=1, Fisher's exact p<0.001). In the overall sample, however, there were no significant differences in adverse effect reports between the 21-mg and 42-mg dosages. Adverse effects that were rated more than moderate in severity and occurred with a frequency >5% included vivid dreams (20.8%), itching/burning at the patch application sites (16.1%), insomnia (9.4%), thirst (8.8%), and dry mouth (5.2%). Based on daily diaries, 93.6% of the total patch doses were received in the 21-mg condition and 87.4% in the 42-mg condition. One participant in the 42-mg patch condition dropped out in the first week because of nausea and vomiting.

Varenicline and bupropion treatments were also generally well tolerated. Overall, 11.5% of participants required dosage reductions in the varenicline-plus-bupropion condition and 24.8% in the varenicline-plus-placebo condition ($\chi^2$=6.61, df=1, Fisher's exact p=0.014). In the overall sample, however, there was no significant difference in the incidence of adverse effects between the two treatment conditions. Adverse effects that were rated more than moderate in severity and occurred with a frequency >5% included headache (9.3%), diaphoresis (8.8%), nasal/sinus irritation (5.9%), change in taste perception (17.2%), dry mouth (10.8%), thirst (15.7%), cough (8.8%), muscle/joint pain/aches (7.4%), heartburn (5.8%), nausea (5.8%), constipation (6.8%), irritability (11.3%), vivid dreams (18.1%), insomnia (13.7%), and anxiety (8.8%). Based on daily diaries, 77.2% of the total number of oral medication doses were taken, which did not differ significantly between the two treatment conditions (78.4% in the varenicline-plus-bupropion condition and 76.0% in the varenicline-plus-placebo condition).

**TABLE 2. Smoking Abstinence at the End of Treatment (Weeks 8–11), by Sex and Baseline Levels of Cigarette Consumption and Nicotine Dependence, in a Study of Combination Treatment With Varenicline and Bupropion**

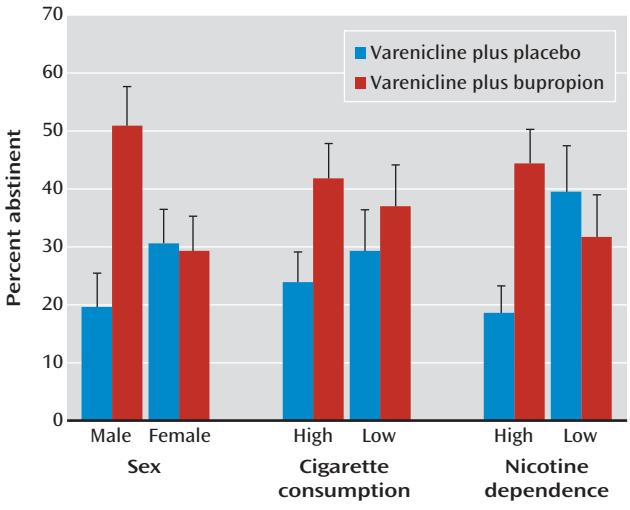
| Variable and Treatment Condition | N | Completed Treatment | | Abstinent | | Odds Ratio | 95% CI | p |
|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | | | |
| **Sex** | | | | | | | | |
| Male | | | | | | 4.26 | 1.73, 10.49 | 0.002 |
| Varenicline plus bupropion | 55 | 36 | 65.5 | 28 | 50.9 | | | |
| Varenicline plus placebo | 46 | 31 | 67.4 | 9 | 19.6 | | | |
| Female | | | | | | 0.94 | 0.43, 2.05 | 0.87 |
| Varenicline plus bupropion | 58 | 36 | 62.1 | 17 | 29.3 | | | |
| Varenicline plus placebo | 62 | 40 | 64.5 | 19 | 30.6 | | | |
| **Baseline cigarette consumption** | | | | | | | | |
| ≥20 cigarettes per day | | | | | | 2.29 | 1.09, 4.81 | 0.03 |
| Varenicline plus bupropion | 67 | 46 | 68.7 | 28 | 41.8 | | | |
| Varenicline plus placebo | 67 | 42 | 62.7 | 16 | 23.9 | | | |
| <20 cigarettes per day | | | | | | 1.42 | 0.58, 3.49 | 0.45 |
| Varenicline plus bupropion | 46 | 26 | 56.5 | 17 | 37.0 | | | |
| Varenicline plus placebo | 41 | 29 | 70.7 | 12 | 29.3 | | | |
| **Baseline nicotine dependence** | | | | | | | | |
| High | | | | | | 3.51 | 1.64, 7.51 | 0.001 |
| Varenicline plus bupropion | 72 | 51 | 70.8 | 32 | 44.4 | | | |
| Varenicline plus placebo | 70 | 24 | 60.0 | 13 | 18.6 | | | |
| Low | | | | | | 0.71 | 0.28, 1.80 | 0.47 |
| Varenicline plus bupropion | 41 | 21 | 51.2 | 13 | 31.7 | | | |
| Varenicline plus placebo | 38 | 29 | 76.3 | 15 | 39.5 | | | |

Seven participants (four in the varenicline-plus-bupropion condition and three in the varenicline-plus-placebo condition) dropped out because of adverse events that were probably related to treatment (e.g., nausea, dizziness, sleep disturbances, anxiety, and depression).

Adherence and adverse effect ratings were also examined for treatment-related sex differences and differences between smokers with high and low nicotine dependence. However, none accounted for the interactive effects of sex or nicotine dependence on treatment efficacy, which remained significant when each adverse effect was included as a covariate in a logistic regression model.

**Weight gain.** By the end of treatment, abstinent smokers gained more weight on average than nonabstainers (2.84 kg compared with 1.02 kg; $F=11.56$, $df=1, 138$, $p<0.001$), with no significant sex or treatment differences. Mean weight gain among successful quitters was 3.05 kg for those receiving varenicline plus bupropion and 2.5 kg for those receiving varenicline plus placebo.

**FIGURE 2. Smoking Abstinence at the End of Treatment (Weeks 8–11), by Sex, Baseline Smoking Rate, and Level of Nicotine Dependence, in a Study of Combination Treatment With Varenicline and Bupropion[a]**




[a] High baseline cigarette consumption was defined as ≥20 cigarettes per day; high baseline nicotine dependence was defined as a score >5 on the Fagerström Test for Nicotine Dependence. Error bars indicate standard deviation, estimated using the normal approximation to the binomial distribution.

## Discussion

The study results showed an overall benefit of adding bupropion treatment to varenicline for nicotine patch nonresponders. Moreover, male smokers and those with high levels of nicotine dependence appeared to have a greater therapeutic response. For these smokers, end-of-treatment abstinence rates among those in the combination treatment condition were more than double those of smokers in the varenicline-plus-placebo condition. This end-of-treatment difference was sustained, although to a lesser extent, at the 6-month follow-up point. In contrast, no statistically significant difference between the two treatments was observed in female smokers or those with lower levels of nicotine dependence, although the 95% confidence

intervals for the odds ratios cannot preclude an effect in these subgroups.

Ebbert et al. (17), in their recently published study evaluating the efficacy of combination treatment with varenicline and bupropion, also reported a significantly higher end-of-treatment abstinence rate for combination treatment with varenicline and bupropion than for varenicline plus placebo, as well as a greater therapeutic effect in smokers with higher dependence levels. No statistically significant sex-by-treatment interaction was detected. However, the design of that study differed in an important respect from ours: all participants were randomly assigned to the two treatments, as opposed to randomizing only the nicotine patch nonresponders.

What potential mechanisms might explain why male smokers who do not achieve sufficient smoking reduction during prequit nicotine patch treatment benefit from receiving combination treatment with varenicline and bupropion? In animal models, some studies have found that males exhibit a greater increase in nicotinic receptor up-regulation than females after chronic nicotine administration (18). Moreover, a recent brain imaging study in smokers found that men, but not women, showed an up-regulation of nicotinic receptors in the striatum, a region important for drug addiction and reward (19). The extent of nicotinic receptor up-regulation, in turn, has recently been shown to predict smoking relapse (20). Therefore, it is conceivable that bupropion and its metabolites, acting as nicotinic receptor antagonists (21), counteract the adverse effects of nicotinic receptor up-regulation in male smokers.

Additionally, sex differences have been reported in striatal dopamine $D_2/D_3$ receptor availability (22), with male smokers showing a down-regulation compared with male nonsmokers and female smokers. Males have also been found to exhibit greater dopamine release in response to drugs of abuse (23), which suggests that they may be more dependent on the dopaminergic stimulation obtained from smoking. Varenicline has been shown to influence striatal dopaminergic transmission, both by enhancing dopamine release (24) and by up-regulating dopamine $D_2/D_3$ receptors (25). However, varenicline, acting on the same receptors as nicotine itself, may provide insufficient dopamine release for nicotine patch nonresponders. Bupropion, in contrast, enhances dopamine transmission through a distinct mechanism, by blocking dopamine reuptake (26). Thus, male smokers who do not respond adequately to nicotine patch treatment may benefit more than female smokers from the action of bupropion on dopamine transmission.

The interaction of treatment with baseline nicotine dependence cannot be attributed to the exclusion of nicotine patch responders, given that the interaction was also observed in the Ebbert et al. (17) study, which did not exclude nicotine patch responders. The interaction is also difficult to explain in terms of the two component treatments, as nicotine dependence level has not generally been reported as a moderating factor in studies that have evaluated varenicline or bupropion individually (27, 28). However, the index of efficacy in these studies has been the comparison of each agent to placebo rather than comparing combination treatment to varenicline plus placebo. Mechanisms underlying the interaction of combination treatment and dependence level will require further investigation.

In addition to showing superior efficacy of combination treatment in specific subpopulations of smokers, our results further validate an adaptive treatment model, in which smokers receive a week of prequit nicotine patch treatment, and based on their reduction in ad lib smoking, either remain on the patch or receive adaptive modifications of treatment. The previous randomized controlled trial in our center (9) showed that approximately 10% of smokers who had a poor initial response to prequit nicotine patch treatment could be rescued by adaptive changes in treatment. In that study, the rescue treatments were varenicline alone or augmentation of nicotine patch treatment with bupropion. The present study extends these results by showing that combination treatment with varenicline and bupropion is an efficacious rescue treatment for male smokers and for highly dependent smokers.

Strengths of the study include the randomized, placebo-controlled design and the use of an adaptive treatment regimen. The study also had limitations. It did not evaluate whether combination treatment with varenicline and bupropion might prove more efficacious than varenicline as an initial treatment for nicotine patch responders; however, our rationale was to avoid the additional risks and side effects of varenicline and bupropion for nicotine patch responders, who have a reasonable chance of quitting using nicotine replacement alone (8). Another limitation was the use of a tailored dosage of precessation nicotine patch therapy and the concurrent use of nicotine replacement and cigarettes during the precessation period, which deviated from current product labeling in the United States. However, the FDA recently issued more liberal guidelines regarding product labeling with respect to concurrent use of nicotine replacement by individuals who continue to smoke (29). Additionally, precessation nicotine patch use is approved in several other countries.

In summary, based on the magnitude of enhancement in abstinence rate and an excellent safety and tolerability profile, the results of this study support the use of combination treatment with varenicline and bupropion for male smokers and highly dependent smokers who do not respond with sufficient smoking reduction during the first week of prequit nicotine patch. Future research should investigate potential biobehavioral mechanisms that may account for the differences in treatment response across subpopulations of smokers.

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