ORIGINAL ARTICLE

Effects of Varenicline and Bupropion Sustained-Release Use Plus Intensive Smoking Cessation Counseling on Prolonged Abstinence From Smoking and on Depression, Negative Affect, and Other Symptoms of Nicotine Withdrawal

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Importance: Given the actions of varenicline tartrate and bupropion hydrochloride sustained-release (SR) on neurobiological targets related to affect and reward, it is thought that the modulation of nicotine withdrawal symptoms may contribute to their effectiveness.

Objective: To assess the relative efficacy of varenicline and bupropion SR plus intensive counseling on smoking cessation and emotional functioning.

Design and Setting: Placebo-controlled randomized clinical trial at a university medical center.

Participants: In total, 294 community volunteers who wanted to quit smoking.

Interventions: Twelve weeks of varenicline, bupropion SR, or placebo plus intensive smoking cessation counseling (10 sessions, for a total of approximately 240 minutes of counseling).

Main Outcome Measures: Prolonged abstinence from smoking and weekly measures of depression, negative affect, and other symptoms of nicotine withdrawal.

Results: Significant differences were found in abstinence at the end of treatment and through the 3-month postquit follow-up visit, favoring both active medications compared with placebo. At the 6-month postquit follow-up visit, only the varenicline vs placebo comparison remained significant. Varenicline use was also associated with a generalized suppression of depression and reduced smoking reward compared with the other treatments, while both active medications improved concentration, reduced craving, and decreased negative affect and sadness compared with placebo, while having little effect (increase or decrease) on anxiety and anger. No differences were noted in self-reported rates of neuropsychiatric adverse events.

Conclusions and Relevance: In a community sample, varenicline exerts a robust and favorable effect on smoking cessation relative to placebo and may have a favorable (suppressive) effect on symptoms of depression and other affective measures, with no clear unfavorable effect on neuropsychiatric adverse events.

Trial Registration: clinicaltrials.gov Identifier: NCT00507728.

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More than 50% of the 45.3 million Americans who still smoke make a serious cessation attempt each year, but only 6% of them remain abstinent for at least 6 months.[1] The provision of pharmacotherapy, particularly when combined with smoking cessation counseling, can substantially improve the success of a cessation attempt.[2] Previous meta-analyses[3-5] of bupropion hydrochloride or varenicline tartrate use have confirmed that both are effective for smoking cessation, and both are considered frontline therapies in clinical practice guidelines.[2]

Bupropion (amfebutamone) is an atypical antidepressant whose mechanism of action is thought to involve modest inhibition of norepinephrine uptake and weaker inhibition of dopamine uptake.[6] In addition, bupropion (particularly its [2S,3S]-hydroxybupropion metabolite) is thought to have an antagonist effect on the $\alpha^4\beta^2$ nicotine acetylcholine receptor.[7] Varenicline is a highly selective partial agonist of the $\alpha^4\beta^2$ nicotine acetylcholine receptor. Its properties include stimulation of

dopamine release in the nucleus accumbens but to a lesser extent than nicotine itself. Also, given its long half-life (24 hours), it is thought to have antagonist properties as well, which may prevent full stimulation of the receptor when nicotine is coadministered,[8] thereby reducing the risk of relapse.

Given the actions of both medications on neurobiological targets related to affect and reward, it is thought that the modulation of nicotine withdrawal symptoms may contribute to their effectiveness. A pooled analysis[9] of withdrawal symptoms during the first week of quitting using data from the phase 3 trials showed that (compared with placebo) both varenicline and bupropion reduced negative affect (overall mean ratings for anger, depression, anxiety, and difficulty in concentrating) using the Minnesota Nicotine Withdrawal Scale.[10] No differences in negative affect using this composite measure were noted between the active drugs. Moreover, in a separate analysis, these differences were limited to individuals abstaining from smoking.[10] Varenicline also reduced craving to a greater extent than bupropion among both abstainers and nonabstainers, and neither medication affected ratings of restlessness, hunger, or insomnia. In addition, both varenicline and bupropion significantly reduced ratings of satisfaction and psychological reward vs placebo (first cigarette following the quit date), with varenicline producing a greater reduction than bupropion.

The present study was a double-blind, placebo-controlled, randomized clinical trial of varenicline tartrate and bupropion hydrochloride sustained-release (bupropion SR), which used a more intensive form of smoking cessation counseling (ie, 10 sessions, for a total of approximately 240 minutes of counseling) than that used in the varenicline phase 3 trials (12 sessions, for a total of approximately 120 minutes of counseling).[11,12] The study was designed with the following 3 objectives in mind: (1) The first goal was to assess the relative efficacy of varenicline and bupropion SR on smoking cessation and symptoms of nicotine withdrawal in conjunction with an intensive form of behavioral counseling, as well as to assess medication compliance and measures of counseling exposure (ie, duration and frequency) actually received by the participants. (2) The second goal was to use multiple and weekly measures of negative affect to help clarify withdrawal pattern differences associated with the use of these medications rather than relying on one composite measure of negative affect as previously noted.[9] This is particularly important given the recent reports associating varenicline use with increased risk of neuropsychiatric adverse events[13] and the need to delineate such effects from those of cessation alone. (3) The third goal of the study was to serve as the parent clinical trial for a series of smaller subinvestigations evaluating psychophysiological and neural predictors of smoking cessation (event-related potentials, acoustic startle, and functional magnetic resonance imaging), along with potential genetic markers mapping onto these predictors. These studies used subsets of individuals participating in the parent clinical trial, and the results of these smaller investigations will be published as separate articles.

METHODS

STUDY DESIGN

The ascertainment of participants is shown in **Figure 1**, and the timeline is shown in **Figure 2**. All participants were screened for eligibility using the following 3-step process: (1) an initial telephone screening, (2) an in-person group orientation visit to more fully explain the study and review the consent form, and (3) a subsequent in-person screening and baseline visit to assess medical and other eligibility criteria and conduct baseline assessments (Figure 2). A total of 294 participants were randomized and exposed to treatment as follows: varenicline (n=86), bupropion SR (n=102), or placebo (n=106). Adaptive randomization (minimization)[14] was used to stratify the groups for sex, race/ethnicity, history of depression, and baseline smoking rate.

Participants

All smokers were volunteers recruited from the Houston, Texas, metropolitan area using radio, newspaper, and television advertisements and public service announcements from August 31, 2006, through October 27, 2010. To be included in the trial, smokers were required to be fluent in English, provide written consent, have a working telephone, be between 18 and 65 years, smoke 5 or more cigarettes per day, have no uncontrolled chronic medical illness, and have a baseline expired carbon monoxide level of greater than 6 ppm. Exclusion criteria were the following: currently taking psychotropic medication, having a lifetime history of a psychotic disorder, having a psychiatric hospitalization within the last year, being involved in any other concurrent smoking cessation activities, having a current psychiatric disorder (including substance abuse except for smoking), scoring moderate or higher on the suicidality subscale of the Mini-International Neuropsychiatric Interview,[15] or having contraindications to the use of varenicline (eg, severe renal impairment) or bupropion SR (eg, history of seizures). This research was approved by The University of Texas MD Anderson Cancer Center Internal Review Board.

Treatment

Pharmacotherapy. All participants took both types of study medication simultaneously on a twice-daily basis. They received active or matching placebo varenicline capsules or active or matching placebo bupropion SR tablets.

Pharmacotherapy was initiated the day after the first treatment visit (Figure 2), 12 to 19 days before the quit date,[1] and followed the recommended dosing for a total of 12 weeks (ie, varenicline tartrate, 0.5 mg/d for days 1-3, followed by 0.5 mg twice a day for days 4-7, and 1 mg twice a day thereafter; or bupropion hydrochloride SR, 150 mg/d for days 1-3, followed by 150 mg twice a day thereafter). Dosage adjustments by the blinded study physician (M.K.-H.) were permitted in an effort to control adverse effects throughout the trial.

This study began recruitment in August 2006. The original trial (cohort 1) involved a comparison of bupropion, nortriptyline hydrochloride, and placebo. With the launch of varenicline in late 2006, the research team for scientific and clinical reasons made a decision to drop the nortriptyline treatment arm of the trial and add a varenicline treatment arm in its place (cohort 2). By that time, 37 individuals had been randomized to bupropion (n=19) or placebo (n=18). Following a delay to obtain institutional review board and data and safety monitoring board approval, we began recruitment for cohort 2 in January 2008. The only difference between the cohorts was that in co-

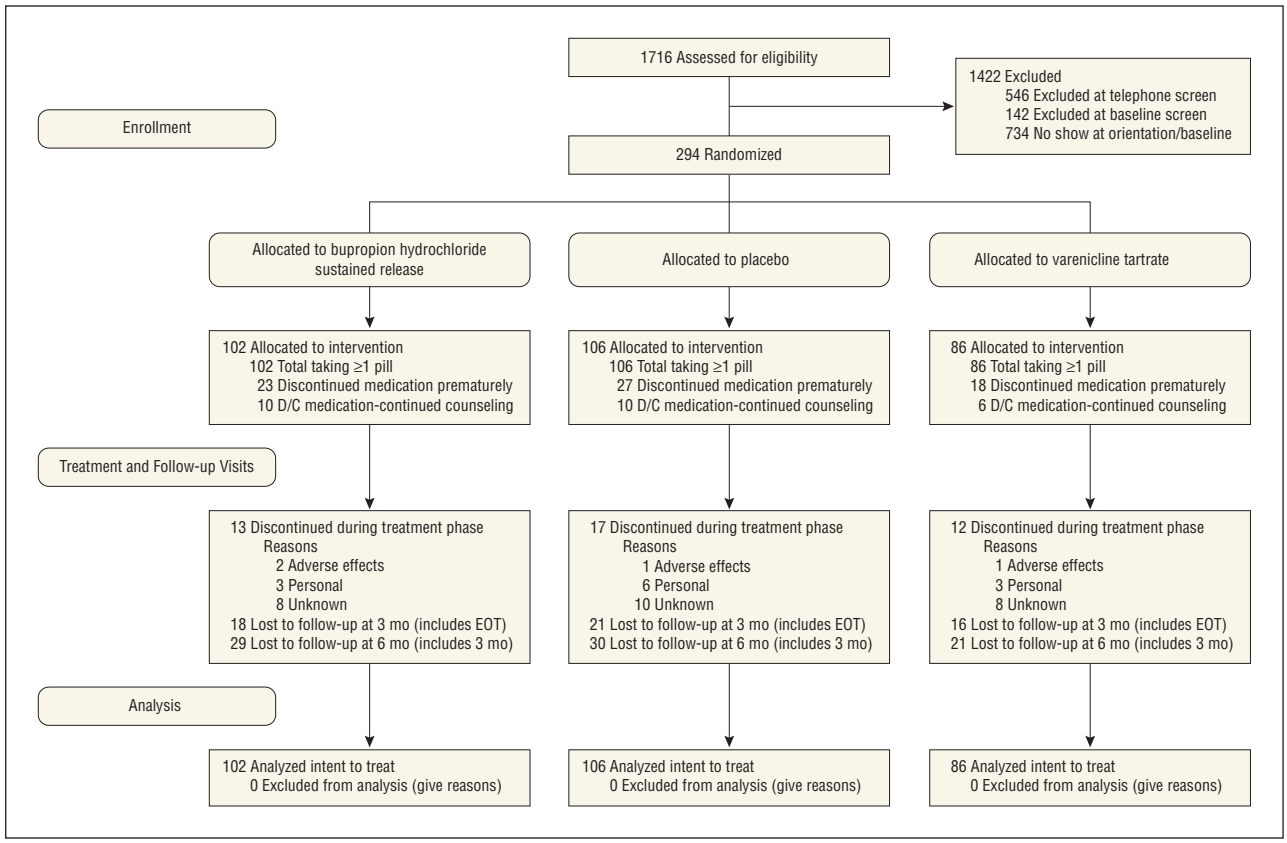

Figure 1. Consolidated Standards of Reporting Trials diagram for patient allocation. D/C indicates discontinued; EOT, end of treatment.

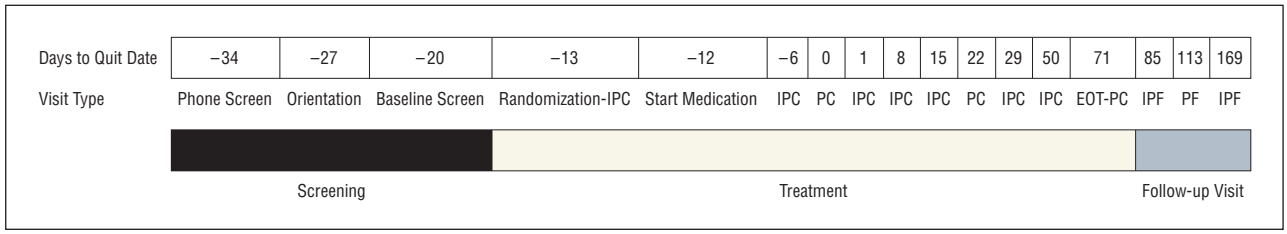

Figure 2. Study visit timeline among cohort 2. EOT indicates end of treatment medication and final counseling call; IPC, in-person counseling; IPF, in-person 3-month and 6-month postquit follow-up visits; PC, phone counseling; and PF, phone 4-month postquit follow-up visit. Cohort 2 is described under Pharmacotherapy in the Methods section.

hort 1, to accommodate the longer dose titration schedule of nortriptyline, all medication was initiated 19 days before quitting and included 3 prequit counseling sessions at each of 3 weekly prequit visits. In cohort 2, medication and counseling were initiated 12 days before quitting and included 2 prequit counseling sessions during a 2-week period. We compared cohorts 1 and 2 on all measures, including demographics, baseline questionnaires, the number of cigarettes per day, and smoking history and dependence. We also compared the bupropion vs placebo abstinence rates across both cohorts for the quit date, 2 weeks following the quit date (2-week grace period), end of treatment (EOT), and all follow-up points using the same definitions of abstinence. No differences were found between the cohorts on any of these comparisons. We also conducted all analyses on cohort 2 alone, and the pattern of results was essentially the same. Given these findings, cohorts 1 and 2 were combined and treated as a single sample throughout this study. For simplicity, all procedures from this point forward are described for cohort 2.

Behavioral Counseling. As shown in Figure 2, all smokers following randomization received individual behavioral smoking cessation counseling conducted via 6 in-person visits and 4 telephone calls during the 12-week active treatment phase. The counseling sessions were approximately 30 minutes and 15 minutes in duration for the in-person and telephone modalities, respectively, yielding a total of 240 minutes of counseling. Counseling involved active effort to prepare for quitting and maintaining abstinence using self-monitoring of smoking before the quit date, identification of high-risk situations for smoking, and the development of coping skills and direct support before and after the quit date. Additional topics included relapse prevention, medication compliance, management of withdrawal symptoms, and stress management and relaxation visualization. Counselors used motivation enhancement strategies based on techniques of motivational interviewing[16] in response to resistance to keeping or resetting a quit date or to maintaining abstinence following the quit date.

Follow-up Visits

Figure 2 summarizes the follow-up visits. Follow-up sessions of 15 minutes' duration were conducted at the 3-, 4-, and 6-month postquit follow-up visits and involved abstinence and other assessments as noted herein.

Assessments

During the baseline screening phase, participants were assessed for health, smoking history, and basic demographics. They were also evaluated for psychiatric disorders using version 5.0 of the Mini-International Neuropsychiatric Interview[15] and for nicotine dependence using the Fagerström Test for Nicotine Dependence.[17,18]

At baseline and at each in-person counseling and follow-up visit, participants completed the Positive and Negative Affect Schedule.[19] They also completed the Wisconsin Smoking Withdrawal Scale (WSWS),[20] which included subscales of anger, anxiety, concentration, craving, hunger, sadness, and sleep. In addition, they completed the Center for Epidemiologic Studies' Depression Scale, which has been used to measure depressive symptoms in community samples.[21,22] The smoking satisfaction and psychological reward subscales of the modified Cigarette Evaluation Questionnaire[23] were also completed by participants who reported smoking between visits.

Abstinence data were collected at all contacts using a timeline follow-back procedure.[24,25] Abstinence outcomes conformed to the Society for Research on Nicotine and Tobacco[26] guidelines. Seven-day point prevalence abstinence was defined as a self-report of no smoking, not even a puff, in the 7 days before the selected time point of interest (eg, EOT or 3-month or 6-month postquit follow-up visits). Continuous abstinence was reported using the following 2 different starting points for assessment: continuous abstinence (2-week grace period) was defined as no smoking, not even a puff, from 2 weeks past the quit date to a future time point. Continuous abstinence (Food and Drug Administration [FDA]) was defined as no smoking beginning with the last 4 weeks of treatment or week 8 of medication in this trial. This measure provides comparability to the results of the phase 3 trials for varenicline and other pharmacotherapies, where continuous abstinence during the last 4 weeks of treatment served as the primary criterion for measuring efficacy and obtaining FDA approval for the pharmacotherapy.

In this study, prolonged abstinence at the EOT served as our primary smoking outcome measure. The common starting point for assessing prolonged abstinence was the end of the 2-week grace period (ie, 2 weeks following the quit date). For prolonged abstinence, relapse was defined by 7 or more consecutive days of smoking or smoking at least 1 cigarette during 2 consecutive weeks from the end of the 2-week grace period to a selected future time point (eg, EOT or 3-month or 6-month postquit follow-up visits).[26] Hence, prolonged abstinence allows a more liberal definition of abstinence than continuous abstinence.

In-person reports of abstinence were verified by expired carbon monoxide of less than 10 ppm. Abstinent participants at the 3- and 6-month postquit follow-up visits who could not return to the clinic and those reporting abstinence at the fourth (EOT) and fifth telephone sessions were asked to provide a saliva cotinine sample by mail. Salivary cotinine values of less than 15 ng/mL were considered to denote abstinence. Participants unavailable for assessment were considered nonabstinent.

Adverse Event Monitoring

Adverse events were monitored at each contact. They were classified and graded using the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria provided by the National Cancer Institute.[27]

Compensation

Participants received compensation for completing assessments. The maximum possible total was $290 across all visits.

STATISTICAL ANALYSIS

Analysis of Demographic and Baseline Variables

For statistical analysis, we used the Tukey studentized range tests (for continuous variables) and Fisher exact tests (for discrete variables). Differences in baseline demographic characteristics were examined by treatment.

Analysis of Abstinence and Treatment of Missing Data

Data collected from the timeline follow-back procedure yielded approximately 64 000 observations (days of data). In the event of missing data (ie, unable to be contacted), all individuals were treated as having smoked during that period (17.0% of the total observations, predominantly after the EOT), except where data were missing between 2 acquired data points that were both coded as abstinent (0.5% of the total observations) or where the first data point was coded as nonabstinent but the second acquired data point was coded as abstinent (0.3% of the total observations). No differences in missing data frequency or the number of individuals lost to follow-up (Figure 1) were noted between the groups. No differences in demographic characteristics (**Table 1**) were observed between those who did or did not attend either of the follow-up sessions, except that those lost to follow-up had significantly fewer years of education ($F_{(1,292)}=7.45$, $P=.006$; mean [SD], 13.4 [1.8] vs 14.2 [2.0] years) and had higher total Fagerström Test for Nicotine Dependence scores ($F_{(1,291)}=5.53$, $P=.02$; mean [SD], 5.1 [2.0] vs 4.4 [2.2]). In every case, the last known status of these individuals lost to follow-up was as a current smoker. All analyses were performed on the intent-to-treat sample (allocated to intervention).

To analyze smoking abstinence, we used commercially available statistical software (SAS PROC LOGISTIC, version 9.2; SAS Institute, Inc). The effect of treatment on each abstinence outcome was evaluated separately for the EOT (primary outcome point) and 3- and 6-month postquit follow-up time points using models that included treatment group (varenicline, bupropion SR, or placebo) as a between-participant fixed effect and included participant as a random effect. All models were tested with the inclusion of sex, race/ethnicity, and study (cohort 1 or cohort 2) as covariates. Because no differences were found by including these covariates, the results are reported for the unadjusted models. We report overall Wald χ^2 values for the effects of treatment, as well as corresponding odds ratios (95% CIs) for all abstinence analyses.

Effects of Treatment on Affect, Craving, and Other Symptoms of Nicotine Withdrawal

To analyze the effects of treatment and time on measures of affect, craving, and other symptoms of nicotine withdrawal (WSWS, Positive and Negative Affect Schedule, and Center for Epidemiologic Studies' Depression Scale), we used mixed-model regression (PROC MIXED, version 9.2; SAS Institute, Inc).[28,29] The model included fixed effects for treatment, time

Table 1. Baseline Demographic and Smoking Characteristics

Variable	Varenicline Tartrate (n = 86)	Bupropion Hydrochloride Sustained-release (n = 102)	Placebo (n = 106)	Total (N = 294)
Baseline Demographic Characteristics, No. (%)				
Race/ethnicity				
African American, non-Hispanic	18 (20.9)	23 (22.5)	22 (20.8)	**63** (21.4)
White, non-Hispanic	50 (58.1)	70 (68.6)	76 (71.7)	**196** (66.7)
Hispanic	10 (11.6)	4 (3.9)	6 (5.7)	**20** (6.8)
Other	8 (9.3)	5 (4.9)	2 (1.9)	**15** (5.1)
Sex				
Male	53 (61.6)	60 (58.8)	67 (63.2)	**180** (61.2)
Female	33 (38.4)	42 (41.2)	39 (36.8)	**114** (38.8)
Marital status				
Married or living with partner	39 (45.3)	45 (44.1)	48 (45.3)	**132** (44.9)
Other	47 (54.7)	57 (55.9)	58 (54.7)	**162** (55.1)
Employment status				
Employed or student	66 (76.7)	80 (78.4)	92 (86.8)	**238** (81.0)
Unemployed	20 (23.3)	22 (21.6)	14 (13.2)	**56** (19.0)
History of depression				
Positive	12 (14.0)	12 (11.8)	10 (9.4)	**34** (11.6)
Negative	74 (86.0)	90 (88.2)	96 (90.6)	**260** (88.4)
Smoking and Other Characteristics, Mean (SD)				
Age, y	43.8 (10.8)	44.0 (9.5)	45.2 (11.0)	44.3 (10.4)
Education, y	14.0 (2.1)	14.0 (2.1)	14.1 (2.0)	14.0 (2.0)
Current smoking rate, cigarettes per day	19.2 (8.5)	20.0 (9.7)	19.7 (9.8)	19.7 (9.4)
Baseline carbon monoxide level, ppm	24.5 (10.8)	25.0 (12.9)	24.1 (11.9)	24.5 (11.9)
Age started smoking, y	18.0 (4.9)	17.6 (4.0)	17.9 (5.9)	17.8 (5.0)
Previous quit attempts, No.	4.2 (4.3)	3.4 (3.3)	3.5 (3.6)	3.7 (3.7)
FTND total score	4.5 (2.2)	4.7 (2.1)	4.4 (2.2)	4.5 (2.2)
CES-D total score	7.0 (6.4)	7.0 (6.0)	8.3 (7.2)	7.5 (6.6)
PANAS				
Negative affect score	14.9 (5.6)	15.8 (4.6)	16.9 (5.8)	15.9 (5.4)[a]
Positive affect score	35.6 (6.7)	35.9 (6.1)	35.7 (6.6)	35.7 (6.4)
WSWS score				
Anger	3.9 (2.6)	4.3 (2.7)	4.3 (2.7)	4.2 (2.7)
Anxiety	7.3 (2.7)	7.5 (3.3)	8.0 (3.2)	7.6 (3.1)
Concentration	3.8 (2.0)	4.0 (2.1)	4.1 (2.3)	4.0 (2.2)
Craving	9.0 (3.1)	9.3 (2.8)	9.1 (2.9)	9.1 (2.9)
Hunger	9.9 (3.6)	9.9 (3.3)	11.1 (3.8)	10.3 (3.6)[a]
Sadness	4.6 (2.6)	4.2 (2.5)	4.7 (2.6)	4.5 (2.6)
Sleep	7.9 (4.2)	9.2 (4.5)	8.6 (4.6)	8.6 (4.5)

Abbreviations: CES-D, Center for Epidemiologic Studies' Depression Scale; FTND, Fagerström Test for Nicotine Dependence; PANAS, Positive and Negative Affect Schedule; WSWS, Wisconsin Smoking Withdrawal Scale.

[a] $P < .05$ for main effect of group.

of assessment, and their interaction term. Time was expressed as postquit days and corresponded to each of the postbaseline in-person and telephone counseling visits (Figure 2) at which data were obtained. Covariates in the model included the baseline (pretreatment) value of each of the corresponding scales for the measure being analyzed, as well as abstinence status (1 indicates abstinent, and 0 indicates nonabstinent) at each of the time points. Significant main effects and interactions were further explored using a least squares mean procedure to contrast pairwise differences among selected means participating in the effect. As described for the analysis of abstinence, we also evaluated an iteration of the basic model that included covariate terms for sex, race/ethnicity, and study (cohort 1 or cohort 2).

Effects of Treatment on Nicotine Reinforcement

To analyze the effects of treatment and time on measures of nicotine reinforcement (modified Cigarette Evaluation Questionnaire), we used the same approach as already described for the analysis of withdrawal symptoms. However, we did not include an effect term for abstinence status because this measure was given only to those who indicated smoking between visits.

Adverse Events

We used the Fisher exact tests to assess adverse events. Differences in the frequency of adverse events were examined by treatment.

RESULTS

Demographic characteristics of the sample are summarized in Table 1. No significant differences between drug groups were noted in any baseline characteristics except for the WSWS hunger subscale and the Positive and Negative Affect Schedule negative affect score.

Table 2. Biochemically Verified Abstinence Rates by Treatment Group Among 86 Participants Receiving Varenicline Tartrate, 102 Participants Receiving Bupropion Hydrochloride Sustained-release (SR), and 106 Participants Receiving Placebo

Variable	Continuous Abstinence, 2-Week Grace Period[a]	Continuous Abstinence, FDA[b]	Prolonged Abstinence[c]	7-Day Point Prevalence[d]
End of Treatment[e]				
Abstinent, No. (%)				
Bupropion SR	37 (36.3)	40 (39.2)	47 (46.1)	50 (49.0)
Placebo	18 (17.0)	20 (18.9)	28 (26.4)	30 (28.3)
Varenicline	37 (43.0)	41 (47.7)	50 (58.1)	50 (58.1)
Odds ratio (95% CI)				
Bupropion SR vs placebo	2.78 (1.46-5.32)	2.77 (1.48-5.20)	2.38 (1.33-4.25)	2.44 (1.37-4.32)
Varenicline vs placebo	3.69 (1.90-7.16)	3.92 (2.06-7.47)	3.87 (2.11-7.11)	3.52 (1.93-6.42)
Varenicline vs bupropion SR	1.33 (0.74-2.39)	1.41 (0.79-2.42)	1.62 (0.91-2.90)	1.44 (0.81-2.58)
Wald χ^2 for group	$\chi^2_2 = 15.87$, $P < .001$	$\chi^2_2 = 18.10$, $P < .001$	$\chi^2_2 = 19.55$, $P < .001$	$\chi^2_2 = 17.95$, $P < .001$
3-Month Postquit Follow-up Visit[f]				
Abstinent, No. (%)				
Bupropion SR	36 (35.3)	38 (37.3)	42 (41.2)	44 (43.1)
Placebo	17 (16.0)	18 (17.0)	27 (25.5)	33 (31.1)
Varenicline	34 (39.5)	37 (43.0)	46 (53.5)	50 (58.1)
Odds ratio (95% CI)				
Bupropion SR vs placebo	2.86 (1.48-5.52)	2.90 (1.52-5.54)	2.05 (1.14-3.69)	1.68 (0.95-2.96)
Varenicline vs placebo	3.42 (1.74-6.72)	3.69 (1.90-7.16)	3.37 (1.83-6.18)	3.07 (1.70-5.56)
Varenicline vs bupropion SR	1.20 (0.66-2.17)	1.27 (0.71-2.28)	1.64 (0.92-2.93)	1.83 (1.02-3.27)
Wald χ^2 for group	$\chi^2_2 = 14.21$, $P < .001$	$\chi^2_2 = 16.22$, $P < .001$	$\chi^2_2 = 15.40$, $P < .001$	$\chi^2_2 = 13.73$, $P < .001$
6-Month Postquit Follow-up Visit[g]				
Abstinent, No. (%)				
Bupropion SR	23 (22.5)	23 (22.5)	27 (26.5)	29 (28.4)
Placebo	15 (14.2)	15 (14.2)	19 (17.9)	25 (23.6)
Varenicline	24 (27.9)	24 (27.9)	33 (38.4)	32 (37.2)
Odds ratio (95% CI)				
Bupropion SR vs placebo	1.77 (0.86-3.62)	1.77 (0.86-3.62)	1.65 (0.85-3.20)	1.29 (0.69-2.40)
Varenicline vs placebo	2.35 (1.14-4.83)	2.35 (1.1-4.83)	2.85 (1.47-5.51)	1.92 (1.03-3.59)
Varenicline vs bupropion SR	1.33 (0.69-2.58)	1.33 (0.68-2.58)	1.73 (0.93-3.21)	1.49 (0.81-2.76)
Wald χ^2 for group	$\chi^2_2 = 5.45$, $P < .06$	$\chi^2_2 = 5.45$, $P < .07$	$\chi^2_2 = 9.80$, $P < .008$	$\chi^2_2 = 4.26$, $P < .12$

Abbreviation: FDA, Food and Drug Administration.
[a] Continuous abstinence (2-week grace period) is no smoking on any day beginning with the end of the 2-week grace period, defined as 2 weeks after the quit day.
[b] Continuous abstinence (FDA) is no smoking on any day beginning with the last 4 weeks of treatment or week 8 of medication.
[c] Prolonged abstinence relapse is defined by smoking for 7 or more consecutive days or by smoking at least 1 cigarette during 2 consecutive weeks beginning with the end of the 2-week grace period.
[d] The 7-day point prevalence is defined as no smoking in the last 7 days of the given period.
[e] Occurs 10 weeks after the quit date and is the end of pharmacotherapy.
[f] Occurs 3 months after the quit date or 2 weeks after the end of pharmacotherapy.
[g] Occurs 6 months after the quit date or 14 weeks after the end of pharmacotherapy.

EFFECTS OF TREATMENT ON ABSTINENCE

Abstinence rates by drug group are listed in **Table 2** for each of the abstinence definitions and for each of 3 time points (EOT and 3- and 6-month postquit follow-up visits). The results for our primary outcome measure of prolonged abstinence revealed overall group differences at EOT and the 3- and 6-month postquit follow-up visits. Abstinence rates for varenicline were significantly higher than those for placebo at all time points, while the bupropion SR vs placebo comparison was significant at EOT and the 3-month postquit follow-up visit but not at the 6-month postquit follow-up visit. Prolonged abstinence rates for varenicline also exceed those of bupropion SR at each time point, although the differences were not statistically significant. Similar results were noted for the analysis of continuous abstinence rates (2-week grace period and last 4 weeks of treatment), as well as the 7-day point prevalence. In all cases, abstinence rates for varenicline were significantly greater than those for placebo at all time points; abstinence rates for bupropion SR were greater than those for placebo, but the comparisons were not significant at 6 months and were marginal for 7-day point prevalence at 3 months ($P = .05$). While varenicline outperformed bupropion SR at every time point by a mean of 5.9% for both continuous abstinence measures, 12.1% for prolonged abstinence, and 10.9% for 7-day point prevalence, the differences were statistically significant only for the 7-day point prevalence comparison at the 3-month postquit follow-up visit.

EFFECTS OF TREATMENT ON AFFECT AND OTHER SYMPTOMS OF NICOTINE WITHDRAWAL AND NICOTINE REINFORCEMENT

As shown in **Figure 3**, main effects of abstinence status indicated that abstainers had lower levels of sadness ($F_{(1,203)} = 34.48$), anxiety ($F_{(1,203)} = 30.05$), and negative affect ($F_{(1,203)} = 14.57$) ($P < .001$ for all) than nonab-

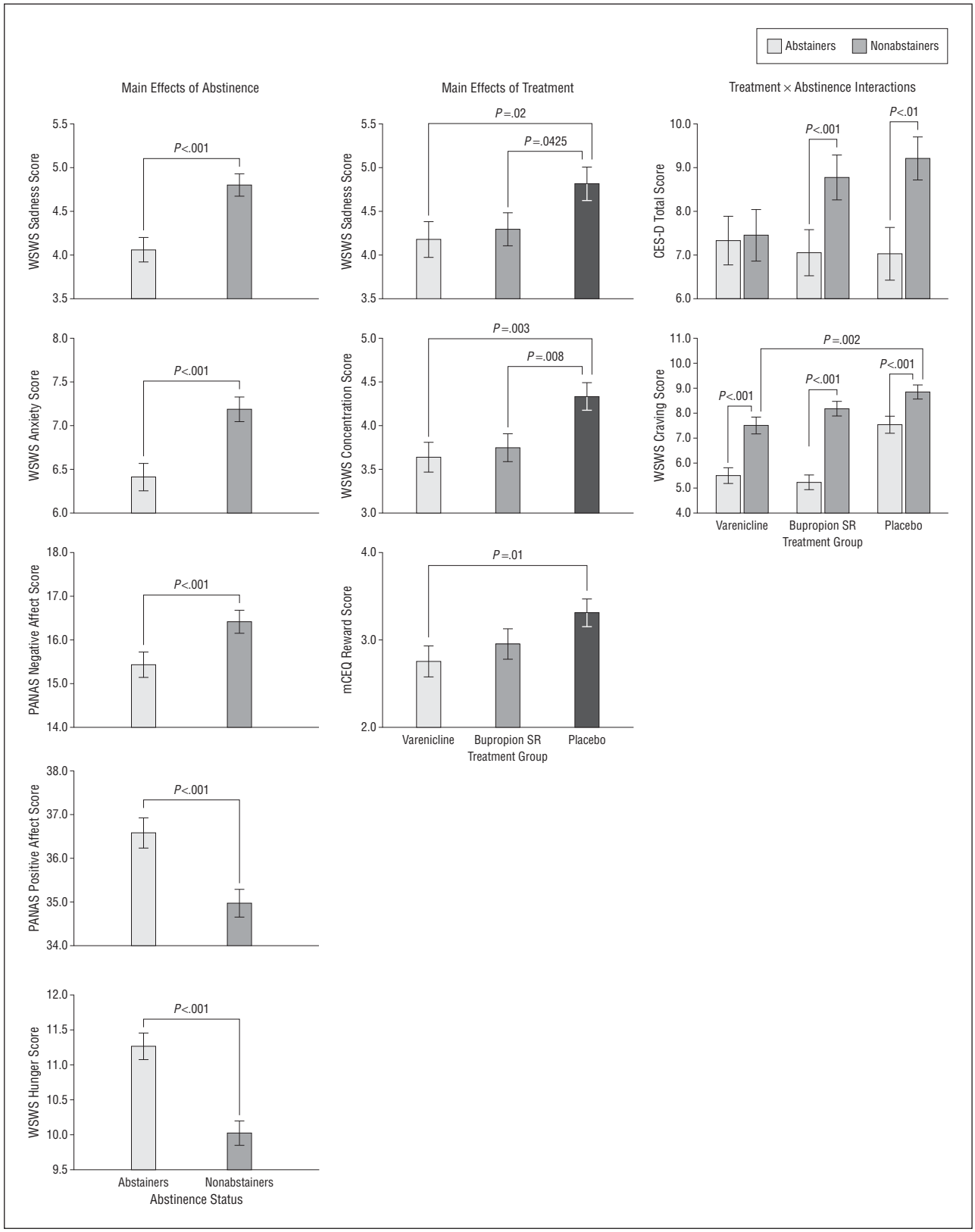

Figure 3. Main effects of abstinence, treatment (varenicline tartrate, bupropion hydrochloride sustained-release [SR], or placebo), and treatment × abstinence interactions. CES-D indicates Center for Epidemiologic Studies' Depression Scale; mCEQ, modified Cigarette Evaluation Questionnaire (in smokers who relapsed); PANAS, Positive and Negative Affect Schedule; and WSWS, Wisconsin Smoking Withdrawal Scale. *P* values are for the actual comparison of individual group means.

stainers. Abstainers demonstrated higher levels of positive affect ($F_{(1,203)}$ = 31.15) and hunger ($F_{(1,203)}$ = 66.03) ($P < .001$ for both) than nonabstainers.

Main effects of treatment (Figure 3) indicated that those taking varenicline or bupropion SR experienced less sadness ($F_{(2,284)}$ = 3.40, P = .03) and showed better concen-

Table 3. Medication Treatment Compliance

Variable	Varenicline Tartrate (n = 86)	Bupropion Hydrochloride Sustained-release (n = 102)	Placebo (n = 106)	Total (N = 294)
Retained for 12-wk treatment, No. (%)	74 (86.0)	89 (87.3)	89 (84.0)	**252** (85.7)
Stopped medication, No. (%)	18 (20.9)	23 (22.5)	27 (25.5)	**68** (23.1)
Stopped medication and continued in counseling[a]	6 (33.0)	10 (43.5)	10 (37.0)	**26** (38.2)
Stopped medication and dropped[a]	12 (66.7)	13 (56.5)	17 (63.0)	**42** (61.8)
Took ≥80% of medication dose, No. (%)	62 (72.1)	79 (77.5)	79 (74.5)	**220** (74.8)
Total pills taken, mean %[b]				
All participants[c]	80.9	83.0	82.8	82.2
Treatment completers only[d]	92.2	94.5	93.7	93.5
Treatment noncompleters only[e]	37.9	43.5	51.1	44.2

[a] Percentage of those who stopped medication.
[b] Total pills assigned minus total pills returned divided by total pills assigned. In the case of premature discontinuation of medication, the total pills assigned and returned would be the same and prorated from the time the medication was discontinued through week 12.
[c] Includes those who stopped medication and remained for counseling plus those who withdrew or failed to return during the 12-week treatment.
[d] Includes all smokers who did not prematurely discontinue medication.
[e] Includes only those smokers who discontinued medication or withdrew sometime during treatment.

tration ($F_{(2,284)}$ = 5.64, P = .004) than those taking placebo. Relapsers taking varenicline experienced less psychological reward from smoking than those taking placebo ($F_{(2,244)}$ = 3.39, P = .04).

Treatment group × abstinence status interactions were assessed (Figure 3). Whereas abstainers experienced significantly lower levels of depression than nonabstainers in the bupropion SR ($F_{(1,201)}$ = 11.36) and placebo ($F_{(1,201)}$ = 14.44) ($P < .001$ for both) groups, they did not differ in the varenicline group. Depression scores were significantly lower for abstainers ($F_{(1,201)}$ = 6.86, P = .009) and nonabstainers ($F_{(1,201)}$ = 5.62, P = .02) in the varenicline group compared with nonabstainers in the placebo group. Notably, while craving was generally higher for nonabstainers compared with abstainers in both drug groups, nonabstainers taking varenicline but not bupropion SR showed significantly less craving than those receiving placebo ($F_{(2,201)}$ = 7.89, $P < .001$).

No significant main effects or interactions were noted for measures of anger, sleep disturbance, or smoking satisfaction. Similarly, no significant interactions were observed for these variables.

TREATMENT COMPLIANCE

Pharmacotherapy

Table 3 summarizes treatment compliance for pharmacotherapy. No differences were noted in the proportion of smokers in each of the groups who were retained for the full 12-week treatment course or in any measure of medication compliance.

Behavioral Counseling

Overall, participants attended a mean (SD) of 5.67 (1.35) in-clinic counseling sessions, resulting in an actual mean (SD) in-clinic counseling dose of 145.87 (35.42) minutes during the course of the study (based on actual session length). A total of 224 participants (76.2%) completed all 6 in-clinic counseling visits. In addition, study participants completed a mean (SD) of 3.43 (1.18) telephone visits, for a mean (SD) telephone counseling dose of 42.56 (14.00) minutes. A total of 200 participants (68.0%) completed all 4 telephone counseling visits. No differences by medication group were observed in treatment attendance for in-person or telephone visits.

ADVERSE EVENTS

In total, 86.1%, 80.4%, and 79.0% of smokers in the varenicline, bupropion SR, and placebo groups, respectively, reported at least 1 adverse event, with no significant differences in overall frequency noted between the groups. As summarized in **Table 4**, placebo use was unexpectedly associated with increased chest pain relative to varenicline, but varenicline use was associated with increased nausea, as expected. Bupropion SR use was associated with increased diarrhea and influenza, and a trend (P = .06) was observed for increased eczema in the varenicline group. No significant group differences were noted for any of the psychiatric or neurological adverse events, including anxiety, irritability, depression, emotional lability, and disturbances in attention, as well as sleep disturbances except for insomnia, which was higher among those receiving bupropion SR (P = .06). Indeed, although not significant, higher levels of anxiety, depression, and attentional disturbances were observed in the placebo group relative to the active drug groups.

Seven serious adverse events were reported during the course of the study, all categorized as such because of patient hospitalization. In the bupropion SR group, the following 3 serious adverse events were noted: bilateral mammoplasty and facial paralysis (regarded as unrelated based on blinded ratings) and syncope (rated as possibly related but could not be verified from hospital records). In the placebo group, 2 serious adverse events were noted, namely, diabetes mellitus (recorded as unlikely related) and chest pain (noted as possibly related). In the varenicline group, 2 serious adverse events were noted,

Table 4. Adverse Event Frequencies That Were Reported by at Least 5% of the Sample, Along With All Adverse Events Reported That Were Classified as Cardiovascular, Gastrointestinal, Neurological, or Psychiatric

Adverse Event	Frequency, No. (%)			
	Varenicline Tartrate (n = 86)	Bupropion Hydrochloride Sustained-release (n = 102)	Placebo (n = 106)	Total (N = 294)
Cardiovascular				
Chest pain or cardiac[a]	1 (1.2)	5 (4.9)	13 (12.3)	**19** (6.5)
Hypertension	3 (3.5)	3 (2.9)	2 (1.9)	**8** (2.7)
Tachycardia or palpitations	1 (1.2)	4 (3.9)	3 (2.8)	**8** (2.7)
Dermatologic				
Eczema[a]	8 (9.3)	6 (5.9)	3 (2.8)	**17** (5.8)
Gastrointestinal				
Nausea[a,b,c]	23 (26.7)	17 (16.7)	8 (7.5)	**48** (16.3)
Diarrhea[b]	9 (10.5)	4 (3.9)	12 (11.3)	**25** (8.5)
Constipation	7 (8.1)	7 (6.9)	4 (3.8)	**18** (6.1)
Gastritis	6 (7.0)	6 (5.9)	5 (4.7)	**17** (5.8)
Flatulence	2 (2.3)	4 (3.9)	2 (1.9)	**8** (2.7)
Vomiting	4 (4.7)	0	2 (1.9)	**6** (2.0)
Hemorrhoids	0	1 (1.0)	1 (0.9)	**2** (0.7)
Blood in stool	0	1 (1.0)	0	**1** (0.3)
Dysphagia	0	1 (1.0)	0	**1** (0.3)
General Disorders				
Appetite increased	8 (9.3)	9 (8.8)	10 (9.4)	**27** (9.2)
Fatigue	4 (4.7)	6 (5.9)	9 (8.5)	**19** (6.5)
Influenza[b]	6 (7.0)	8 (7.8)	2 (1.9)	**16** (5.4)
Head, Neck, and Oral				
Taste perversion	5 (5.8)	4 (3.9)	7 (6.6)	**16** (5.4)
Toothache	3 (3.5)	7 (6.9)	5 (4.7)	**15** (5.1)
Musculoskeletal				
Musculoskeletal pain	12 (14.0)	11 (10.8)	13 (12.3)	**36** (12.2)
Neurological				
Insomnia[b]	20 (23.3)	32 (31.4)	21 (19.8)	**73** (24.8)
Headache	10 (11.6)	15 (14.7)	12 (11.3)	**37** (12.6)
Drowsiness or hypersomnia	5 (5.8)	4 (3.9)	8 (7.5)	**17** (5.8)
Sensory disturbance	1 (1.2)	1 (1.0)	2 (1.9)	**4** (1.4)
Paresthesia	1 (1.2)	0	1 (0.9)	**2** (0.7)
Cerebrospinal fluid leakage	1 (1.2)	0	0	**1** (0.3)
Psychiatric				
Irritability	12 (14.0)	16 (15.7)	17 (16.0)	**45** (15.3)
Abnormal dreams	13 (15.1)	6 (5.9)	11 (10.4)	**30** (10.2)
Anxiety symptoms	7 (8.1)	8 (7.8)	15 (14.2)	**30** (10.2)
Depression	6 (7.0)	8 (7.8)	14 (13.2)	**28** (9.5)
Disturbance in attention	3 (3.5)	7 (6.9)	16 (15.1)	**26** (8.8)
Restlessness	1 (1.2)	5 (4.9)	6 (5.7)	**12** (4.1)
Emotional lability	2 (2.3)	3 (2.9)	4 (3.8)	**9** (3.1)
Panic attack	1 (1.2)	0	2 (1.9)	**3** (1.0)
Elevated mood	0	0	1 (0.9)	**1** (0.3)
Intrusive thoughts	0	0	1 (0.9)	**1** (0.3)
Reduced inhibition	0	1 (1.0)	0	**1** (0.3)
Suicidal ideation	0	0	1 (0.9)	1 (0.3)
Respiratory				
Shortness of breath	6 (7.0)	7 (6.9)	13 (12.3)	**26** (8.8)
Increased coughing	7 (8.1)	8 (7.8)	5 (4.7)	**20** (6.8)
Rhinitis and Upper Respiratory Tract Symptoms				
Rhinitis	18 (20.9)	28 (27.5)	25 (23.6)	**71** (24.1)
Sore throat	4 (4.7)	6 (5.9)	9 (8.5)	**19** (6.5)

[a] Significant difference between varenicline and placebo.
[b] Significant difference between bupropion sustained-release and placebo.
[c] Significant difference between varenicline and bupropion sustained-release.

chest pain in one participant (regarded as unlikely related) and psychiatric hospitalization in another participant (noted as possibly related). The latter participant was found to have a psychiatric history, which was denied at intake, and had taken an intentional nonstudy drug overdose that he described as not associated with an intent to die but rather an attempt to gain attention from his girlfriend. A single adverse event of suicidal ideation was also noted in the placebo group.

COMMENT

The results of this study generally confirm the findings from previous smoking cessation trials in which both varenicline and bupropion have been shown to be more effective than a placebo control and varenicline has been shown to be more effective than bupropion.[3,30] Across various definitions of abstinence, varenicline consistently outperformed placebo at every time point. Bupropion SR consistently outperformed placebo through the 3-month postquit follow-up visit for all but the 7-day point prevalence measure. While varenicline consistently outperformed bupropion SR, the differences were significant only at the 3-month postquit follow-up visit for 7-day point prevalence abstinence. Our results are similar to the patterns observed in the substantially larger phase 3 trials of varenicline,[11,12] although the bupropion vs placebo and varenicline vs bupropion comparisons remained significant at all time points in those studies.

Three major differences are noted between this trial and previous trials for varenicline and bupropion, including the pivotal trials for varenicline that included a bupropion active control.[11,12] First, smokers in this trial were receiving study medication 12 to 19 days before quitting as opposed to 7 days in the phase 3 trials, which also resulted in a corresponding increase in the weekly prequit counseling sessions. However, it is unlikely that the small increase in prequit medication use would have ultimately contributed to study differences because a varenicline study[31] varying prequit medication exposure found results similar to those of the phase 3 trials.

Second, smokers were also assigned to receive a total of 240 minutes of counseling, of which they received a mean of 188.13 minutes based on actual session length, or about 78.4% of the intended dose. This was a longer allocation than that used in the phase 3 trials for varenicline (120 minutes), although no comparable compliance statistics are available. The abstinence rates and effect sizes from investigations using comparable abstinence definitions suggest that continuous abstinence (FDA) rates at 6 months in our study averaged about 4.5 points higher across groups than those observed in previous investigations, which resulted in a slightly (albeit consistently) lower odds ratio than the earlier trials for each of the 2-way drug comparisons.[3-5,11,12] While increased counseling may have raised the overall cessation rates slightly, the absolute differences between the drug groups across the trials remained roughly the same.

Third, our sample size provided adequate power for assessing our primary outcome of prolonged abstinence at EOT (ie, $\beta = .99$ for differences relative to placebo for varenicline and $\beta = .84$ for differences relative to placebo for bupropion SR) but modest power for detecting drug group differences ($\beta = .74$). Prolonged abstinence was selected as the primary end point because this study was part of a larger investigation of psychophysiological predictors of smoking cessation that focused on comparisons with placebo at proximal end points. The effects for varenicline vs placebo were robust, but our comparisons involving bupropion SR, while in the expected direction, were limited because of the sample size needed to detect smaller treatment effects.

An important contribution of this study is a cluster of findings involving measures of depression, negative affect, and other symptoms of nicotine withdrawal. Abstinence alone was associated with improved affect (ie, increased positive affect and decreased sadness, anxiety, and negative affect) relative to nonabstinence; however, among those taking varenicline, scores for depression did not differ as a function of abstinence as they did for bupropion SR and placebo, and scores on this measure were lower for varenicline nonabstainers than for those in the other groups. Smokers taking varenicline and bupropion SR also reported overall lower levels of sadness (on the WSWS) relative to those receiving placebo. In addition, among relapsers, only those in the varenicline group reported decreased psychological reward from smoking. We found no drug-related differences in weekly measures of anxiety or anger (on the WSWS) or in spontaneously reported psychiatric adverse events. A possible suicide attempt without clear intent was reported in the varenicline group. Although drug effects cannot be completely ruled out, there were extenuating circumstances such as an emotional precipitating event, a history of psychiatric disturbance, and the absence of other prior related affective adverse events (ie, depression), which reduce this probability.

Together, these findings suggest that varenicline use might be associated with a generalized suppression of some symptoms of negative affect during smoking cessation, particularly those related to depression, and has little effect on anxiety and anger. What is particularly noteworthy in this trial is that assessments of affective functioning and nicotine withdrawal were conducted on a weekly basis using standardized instruments. The results using this type of ongoing assessment are informative given the postmarketing reports associating varenicline use with increased depression and related affective disturbances, such as anxiety and hostility.[13,32] Moreover, no differences between the groups were noted in self-reported neuropsychiatric adverse events, specifically in anxiety, irritability, depression, emotional lability, or disturbances in attention. In fact, while not significant, the rates for several of these symptoms were higher in the placebo group. This is most likely due to the effects of unmedicated nicotine withdrawal and points to the difficulty in delineating adverse events in this area that are caused by drug effects compared with smoking cessation. Relative to placebo, both active drugs resulted in improved concentration, consistent with the affective data presented herein, as well as reduced craving. Our analysis of weekly measures of affective and cognitive functioning (concentration) controlled for ab-

stinence and provides an increased degree of confidence that, in fact, medication may be attenuating this cluster of neuropsychiatric and nicotine withdrawal symptoms rather than causing a worsening of these conditions. A limitation of our findings that should be noted is that the inclusion and exclusion criteria used in our community-based sample are similar to those used in the phase 3 trials of varenicline, which excluded smokers with current psychiatric illness. The presence of a psychiatric disorder could moderate the risk of neuropsychiatric symptoms, although a trial among patients with schizophrenia did not find this to be the case.[33]

As expected, examination of other voluntarily reported adverse event data showed that varenicline use was associated with increased reports of nausea and that bupropion SR use was associated with increased reports of insomnia. Neither medication differed from placebo for any other symptom of sleep disturbance. Smokers in the placebo group unexpectedly also reported more chest pain than those in either active treatment group, which is inconsistent with a recent meta-analysis[34] of varenicline that suggested an increased risk of cardiovascular sequelae in response to varenicline pharmacotherapy, although our sample size is far too small for any meaningful comparison of cardiovascular events. It is unlikely that any treatment-related differences in this study are due to differential exposure to pharmacotherapy or counseling because compliance measures did not differ across groups.

In conclusion, the results of this study point to a robust and consistently favorable effect of varenicline on smoking cessation relative to placebo. While in the expected direction, less consistent effects were noted for the comparisons involving bupropion SR. Varenicline also had little effect on anxiety and anger, had a suppressive effect on symptoms of depression, and (like bupropion SR) reduced withdrawal-related sadness and negative affect. Such findings run counter to current reports of enhanced neuropsychiatric symptoms associated with varenicline therapy. A limitation of our study is the sample size for detecting drug-related differences. Furthermore, this trial used a sample similar to that in the phase 3 trials, which limits the generalizability of our affective findings to the population of smokers at large, particularly among those with current psychiatric disorders.

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