

Comparative Effectiveness of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics

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Background: Randomized efficacy clinical trials conducted in research settings may not accurately reflect the benefits of tobacco dependence treatments when used in real-world clinical settings. Effectiveness trials (eg, in primary care settings) are needed to estimate the benefits of cessation treatments in real-world use.

Methods: A total of 1346 primary care patients attending routine appointments were recruited by medical assistants in 12 primary care clinics. Patients were randomly assigned to 5 active pharmacotherapies: 3 monotherapies (nicotine patch, nicotine lozenge, and bupropion hydrochloride sustained release [SR]) and 2 combination therapies (patch + lozenge and bupropion SR + lozenge). Patients were referred to a telephone quit line for cessation counseling. Primary outcomes included 7-day point prevalence abstinence at 1 week, 8 weeks, and 6 months after quitting and number of days to relapse.

Results: Among 7128 eligible smokers (≥ 10 cigarettes per day) attending routine primary care appointments, 1346 (18.9%) were enrolled in the study. Six-month abstinence rates for the 5 active pharmacotherapies were the

following: bupropion SR, 16.8%; lozenge, 19.9%; patch, 17.7%; patch + lozenge, 26.9%; and bupropion SR + lozenge, 29.9%. Bupropion SR + lozenge was superior to all of the monotherapies (odds ratio, 0.46-0.56); patch + lozenge was superior to patch and bupropion monotherapies (odds ratio, 0.56 and 0.54, respectively).

Conclusions: One in 5 smokers attending a routine primary care appointment was willing to make a serious quit attempt that included evidence-based counseling and medication. In this comparative effectiveness study of 5 tobacco dependence treatments, combination pharmacotherapy significantly increased abstinence compared with monotherapies. Provision of free cessation medications plus quit line counseling arranged in the primary care setting holds promise for assisting large numbers of smokers to quit.

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TOBACCO USE CONTINUES TO be a significant health threat, with approximately 438 000 smoking-related deaths occurring annually in the United States.¹ However, substantial progress has been made in the last 40 years in reducing smoking prevalence from 42.4% in 1965 to 20% in 2007.^{2,3} In part, these declines are the result of the development of effective cessation treatments. For example, meta-analyses of 86 cessation medication studies in the US Public Health Service (PHS) clinical practice guideline *Treating Tobacco Use and Dependence: 2008 Update*⁴ (hereafter, 2008 PHS Guideline) confirmed the efficacy of all 7 Food and Drug Administration (FDA)-approved medications as well as nortriptyline hydrochloride, clonidine, and various combina-

tion therapies (eg, bupropion hydrochloride sustained release [SR] + nicotine patch). Yet, most data on cessation pharmacotherapies come from placebo-controlled efficacy trials conducted under ideal circumstance (eg, with motivated volunteers, inducements for participation, extensive participant contact), with few directly contrasting multiple pharmacotherapies in head-to-head comparisons. Even fewer studies have conducted such head-to-head tests in real-world clinic settings.⁴

The primary care clinic is an ideal environment in which to study comparative effectiveness of cessation treatments. First, many smokers report being receptive to advice from their primary care provider (PCP) to quit smoking.⁵ Second, more than 70% of smokers visit their PCP annually.⁶ Third, health considerations are

especially salient in a clinical setting, making patient visits “teachable moments” to intervene with tobacco users and, in addition, a majority of primary care patients who smoke express interest in cessation treatment and many prefer more intensive treatment.⁷ Finally, primary care–based cessation treatment is cost-effective, even when cessation medications are provided at no cost.⁸

Clinician intervention with smokers (eg, brief counseling, cessation medication) is recommended by the 2008 PHS Guideline update⁴ and has been shown to increase the likelihood of successful quitting.^{4,9} However, PCPs typically have limited time to deliver cessation counseling and clinics often do not have other clinical staff available to provide such services. Telephone tobacco quit lines can serve as “treatment extenders” by providing cost-effective counseling in conjunction with the initial intervention provided by PCPs.¹⁰⁻¹² In fact, recent research by Borland and colleagues¹³ demonstrated that referral of primary care smokers to a quit line (to augment in-clinic treatment) more than doubled cessation rates at 1 year compared with the standard in-clinic PCP-based treatment.

The present study was designed to address 2 primary questions: (1) When smoking cessation medication and counseling are made available at no cost in the primary care setting, what percentage of eligible smokers will make a quit attempt? and (2) What are the relative short- and long-term abstinence rates of 5 different smoking cessation pharmacotherapies when used in “real-world” primary care settings? To answer these questions, we recruited 1346 smokers in 12 primary care clinics to participate in a randomized effectiveness trial comparing 5 cessation pharmacotherapy treatments in combination with telephone counseling provided through a state tobacco quit line. The 5 pharmacotherapy treatments included 3 FDA-approved monotherapies (nicotine patch, bupropion SR, and nicotine lozenge) and 2 combination therapies (bupropion SR + lozenge, patch + lozenge).

The nicotine patch was included because it is widely used,¹⁴ available over the counter (OTC), easy to use, and efficacious (odds ratio [OR], 1.9 [2000 PHS Guideline¹⁵]). Bupropion SR was included because it was found to be efficacious in 2 large multicenter clinical trials^{16,17} at the time of the study design, and it has been found in some studies to be more efficacious than the nicotine patch.^{17,18} The nicotine lozenge was included because it was a relatively new OTC nicotine replacement therapy (NRT), with promising early results (for 2 mg: OR, 2.0; for 4 mg: OR, 2.8).¹⁹

In addition, we tested 2 combination therapies: bupropion SR + lozenge and patch + lozenge. We included bupropion SR + lozenge because we hypothesized that the use of a nonnicotine cessation medication (bupropion) combined with an ad libitum NRT (lozenge) would boost cessation rates over those produced by monotherapies. Likewise, we included patch + lozenge because the 2000 PHS Guideline¹⁵ found that combination NRT was more efficacious than a single NRT.¹⁵ Presumably, users of the patch + lozenge would have the benefit of steady state nicotine levels via the patch that could be augmented by lozenge use when urges or cravings to smoke are especially intense. We hypothesized that patch + lozenge would boost cessation rates over those produced by monotherapies.

The 5 pharmacotherapy treatments in the present study were also tested concurrently in a separate placebo-controlled randomized clinical trial (RCT) conducted by our research team as part of the National Institutes of Health (NIH)-funded University of Wisconsin Transdisciplinary Tobacco Use Research Center (TTURC) grant. That RCT (reported elsewhere²⁰) randomized 1504 adult smokers (recruited from the community) to the same active medication conditions or placebo; all participants received individual counseling. Results for this efficacy RCT showed that all 5 active pharmacotherapy conditions were efficacious relative to placebo and that the patch + lozenge treatment had the largest OR and was superior to the monotherapies. Although this RCT differed in several ways from the present study (eg, type of counseling), these 2 independent studies provide a unique opportunity to assess comparative effectiveness for the same 5 pharmacotherapy treatments in both an efficacy RCT and a real-world effectiveness environment.

METHODS

PARTICIPANTS

Participants were 1346 smokers recruited in 12 Aurora Health Care primary care clinics in eastern Wisconsin from October 2005 through May 2007. **Figure 1** (CONSORT [Consolidated Standards of Reporting Trials] diagram) provides detailed information about study recruitment, enrollment, and follow-up. Primary inclusion criteria included (1) 18 years or older; (2) 10 or more cigarettes per day (CPD) for the past 6 months; (3) motivated to quit smoking; and (4) if female, willing to use an acceptable contraception while using the study medication. Primary exclusion criteria included (1) history of seizures or convulsions, bipolar disorder, psychosis, bulimia, or anorexia nervosa; (2) head injury requiring hospitalization; (3) myocardial infarction in past month; (4) current use of bupropion or use of a monoamine oxidase (MAO) inhibitor in the previous 2 weeks; (5) blood pressure greater than 160/100 mm Hg; (6) allergy to any of the study medications; (7) serious thoughts of self-harm in the previous 2 weeks; (8) drug or alcohol dependence in the past 6 months; and (9) currently pregnant or breastfeeding or planning to become pregnant within the next 3 months. This study was approved by the institutional review boards of Aurora Health Care and the University of Wisconsin. Participants received free treatment in exchange for study participation.

RECRUITMENT AND ENROLLMENT PROCEDURES

At each of the 12 clinics, clinic staff (medical assistants [MAs] and PCPs) were trained in study recruitment and other related procedures. The role of MAs included screening for tobacco use, advising smokers to quit, assessing willingness to quit smoking, and determining initial study eligibility. The MAs also documented each clinical encounter in the electronic health record and, for smokers interested in study participation, notified the PCP of the patient's interest, gave the patient the study consent form to review, and faxed a Wisconsin Tobacco Quit Line (WTQL) referral form to the study office. The MAs assessed 45 501 patients (Figure 1); some patients were assessed multiple times (because of separate clinic visits) for a total of 72 435 clinic visits.

Each interested patient was medically evaluated by his or her physician who documented eligibility on a study medical clearance form that provided specific exclusionary criteria. For

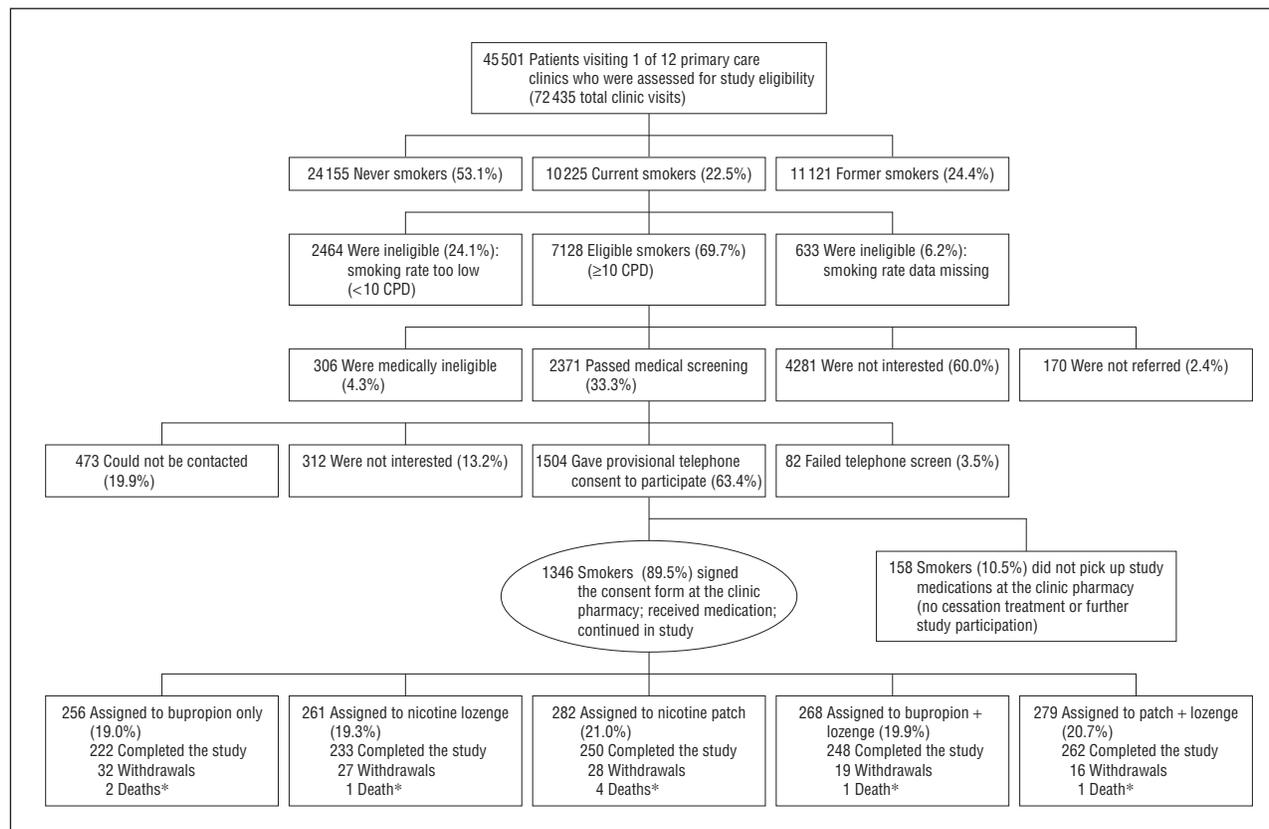


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. CPD indicates cigarettes per day. *Deaths were not related to study medication. Bupropion was administered as bupropion hydrochloride sustained release.

patients meeting inclusion and exclusion criteria, the medical clearance form was faxed to the central study research office. Patients were then called within 1 business day of their clinic visit by a research assistant who explained the study and obtained verbal informed consent. The research assistant then conducted a study assessment interview, obtained contact information, and faxed information to the WTQL to arrange for telephone-based cessation counseling. In addition, the research assistant randomized the patient to treatment, discussed and set a quit date, provided instructions about picking up medication at the clinic pharmacy, faxed a prescription to the clinic pharmacy, and entered the prescription into the electronic health record. During this same call, the patient was informed which medication he or she would receive.

A total of 1504 patients provided provisional consent to participate in the study and were randomized to a medication condition. Of these 1504 patients, 1346 picked up their study medication at the pharmacy and continued in the study; 158 elected not to pick up their study medication and had no further study participation. At the clinic pharmacy, the pharmacist obtained written consent, dispensed prepackaged study medication, and sent a fax to the central research office verifying that study medication was dispensed to the patient.

MEDICATION INTERVENTIONS

Participants received free open-label medications. Bupropion SR was up-titrated as per labeling during the week before quitting to the full dose (150 mg twice daily) and continued for 8 weeks after quitting. The nicotine patch was used as follows: the 21-mg patch was used for postquit weeks 1 to 4, the 14-mg patch for weeks 5 to 6, and the 7-mg patch for weeks 7 to 8. Nicotine lozenge treatment (4 mg if the first cigarette of the day was smoked

within 30 minutes after waking, 2 mg otherwise) consisted of 1 lozenge every 1 to 2 hours for the first 6 weeks after quitting, 1 lozenge every 2 to 4 hours during weeks 7 to 9, and 1 lozenge every 4 to 8 hours during weeks 10 to 12. Adverse event data were not systematically assessed because all medications are FDA-approved and the study was designed to be similar to real-world cessation practice where adverse events are not systematically collected. Participants were instructed to contact their PCP for medication-related questions or problems.

SMOKING CESSATION COUNSELING

Cessation counseling was provided by the WTQL following fax referral from the study office. WTQL counselors attempted to proactively contact all study participants to conduct an initial assessment to guide the subsequent counseling. Study participants could elect to receive up to 4 additional counseling calls and could call for additional support if so desired. Cessation counseling elements included those shown to be efficacious in the 2000 PHS Guideline¹⁵ including problem-solving/skills training (eg, recognition of high-risk situations, improving coping skills) as well as support via encouragement to quit, expression of willingness to help, and reinforcement for progress.

PRIMARY AND SECONDARY OUTCOMES

Smoking status was assessed during follow-up telephone interviews at 12 and 24 weeks after quitting using a smoking calendar and the timeline followback method²¹; approximately 75% of patients were successfully contacted for telephone follow-up interviews. Primary postquit outcomes included 7-day point prevalence abstinence (0, abstinent; 1, smoking) at 1 week

Table 1. Descriptive Statistics for Sociodemographic and Smoking History Variables for the Total Sample and by Treatment Group

Characteristic	Total Sample (N=1346)	Bupropion ^a (n=256)	Nicotine Lozenge (n=261)	Nicotine Patch (n=282)	Bupropion ^a + Lozenge (n=268)	Nicotine Patch + Lozenge (n=279)	P Value
Age, mean (SD), y	44.3 (12.1)	44.0 (11.6)	42.9 (11.7)	44.5 (12.4)	45.4 (12.2)	44.8 (12.4)	.17
Female, No. (%)	753 (56)	143 (56)	142 (54)	158 (56)	152 (57)	158 (57)	.99
Married	54	53	50	57	55	55	.60
Employed	72	72	76	69	73	73	.59
Race, %							
White	87	88	87	86	88	88	.92
African American	10	9	9	9	10	10	
Other	3	3	4	5	2	2	
Hispanic	2	2	1	3	3	2	.42
Education, %							
Not a high school graduate	13	13	13	15	12	10	.17
High school graduate	44	48	49	38	44	43	
More than high school	33	39	38	47	44	47	
Age at first cigarette, mean (SD), y	14.4 (3.9)	14.5 (4.4)	14.3 (3.5)	13.9 (4.1)	14.4 (3.8)	14.8 (3.7)	.10
Cigarettes smoked per day, mean (SD), No.	20.3 (8.8)	20.4 (8.7)	19.9 (9.4)	19.9 (8.5)	20.7 (8.3)	20.4 (8.8)	.79
FTND score, mean (SD)	5.1 (2.1)	5.0 (2.1)	5.0 (2.2)	5.3 (2.1)	5.2 (2.0)	5.0 (2.1)	.43
Previous quit attempts, mean (SD), No.	5.7 (9.3)	5.9 (10.5)	5.3 (6.7)	5.5 (8.3)	5.4 (9.9)	6.3 (10.7)	.67

Abbreviation: FTND, Fagerström test for nicotine dependence.²⁵

^aBupropion was administered as bupropion hydrochloride sustained release.

and 8 weeks (based on the week 12 interview) and at 6 months (based on the week 24 interview). For purposes of survival analysis, the number of days to relapse (defined as latency to smoke on 7 consecutive days after the quit day) in the first 6 months after quitting (0-182 days) was computed. Secondary outcomes included WTQL use (0, no use; 1, at least 1 call completed) and total minutes of WTQL counseling.

VALIDITY OF SELF-REPORTED SMOKING STATUS

While RCT efficacy studies commonly obtain biochemical verification of abstinence at key study end points, effectiveness studies such as the current study typically rely only on self-reported abstinence to maximize the “real-world” aspect of the study. In addition, collection of biological samples can be logistically challenging and costly in effectiveness studies. Self-reported abstinence in effectiveness studies has been recommended by the Society for Research on Nicotine & Tobacco (SRNT) Subcommittee on Biochemical Verification²² and, consistent with this recommendation, biochemical verification of abstinence was not obtained in the present study.

SAMPLE SIZE

Sample size was based on estimated point prevalence abstinence rates at 6 months derived from efficacy meta-analyses^{15,23} and relevant effectiveness studies^{18,24} available at the time of study design. Power analyses showed that a sample size of 1320 (n=264 per treatment condition) would be adequate to detect differences of at least 13% for 6 comparisons testing the predicted superiority of the combination medication conditions vs the monotherapy conditions at a power of 0.80 (2-sided tests, Bonferroni corrected).

RANDOMIZATION

Smokers were randomized to the 5 treatment conditions within each clinic with blocking on sex and self-identified race (white/nonwhite) to ensure the balance of women, men, whites, and nonwhites allocated to each treatment condition.

STATISTICAL METHODS

All comparative analyses were conducted on an intent-to-treat basis. All smokers who were randomized to a treatment and who picked up study medications were included in the analyses; participants with missing data on smoking status were considered to be smoking. Group differences in abstinence rates were tested using multivariate logistic regression with fixed effects for treatment, sex, race (0, nonwhite; 1, white), and clinic (treated as a fixed effect because the unit of randomization was the patient rather than the clinic). For each of the 3 study end points, 6 primary group comparisons of point prevalence abstinence were tested: bupropion SR + lozenge vs each of the 3 monotherapies and patch + lozenge vs each of the 3 monotherapies. We also conducted corresponding Cox regression survival analyses of risk of relapse with fixed effects for treatment, clinic, sex, and race included in the model. All tests were 2-sided; Bonferroni-corrected P values were used to control for familywise error at each end point (with 6 comparisons and an initial α level of .05 [$P=.008$ after Bonferroni correction]). All estimates (eg, ORs) and 95% confidence intervals were computed using SPSS for Windows version 16 (SPSS Inc, Chicago, Illinois) or SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Figure 1 shows that 45 501 primary care patients were assessed for study eligibility and that 10 225 were current smokers. Among current smokers, there were 7128 eligible (≥ 10 CPD) smokers (69.7% of all smokers). Of those eligible, 1346 (18.9%) were randomized to treatment, representing approximately 1 in 5 eligible smokers. **Table 1** provides descriptive statistics for sociodemographic and smoking variables for the total sample and by treatment group. There were no statistically significant group differences on any of these variables. **Table 2** provides descriptive statistics for selected sociodemographic and smoking variables for each of the 12 primary care clinics. These statistics show that the participating clinics represented a

Table 2. Descriptive Statistics for the Aurora Health Care (AHC) Primary Care Clinics

AHC Clinic Name, City Location (All in Wisconsin)	Total Patients, No. (%)	Patients, %				Mean (SD)		
		Female	White	Black	Employed	Age, y	FTND	CPD
AHC–Silver Spring, Milwaukee	110 (8.2)	66	21	75	57	45.0 (10.9)	5.1 (2.0)	16.6 (7.2)
AHC–Mayfair, Wauwatosa	70 (5.2)	54	79	19	71	48.1 (12.2)	5.0 (2.3)	20.2 (9.4)
AHC–Sheboygan Clinic, Plymouth	293 (21.8)	53	97	0	82	42.5 (12.0)	4.9 (2.2)	19.9 (9.1)
AHC, Waukesha	47 (3.5)	64	89	4	83	41.4 (11.0)	5.3 (2.1)	20.5 (7.3)
AHC, Edgerton	64 (4.8)	39	91	2	78	46.7 (11.7)	5.1 (2.1)	21.1 (9.1)
AHC Sheboygan Clinic, Sheboygan	230 (17.1)	52	95	1	74	44.0 (12.3)	5.1 (1.9)	21.6 (8.8)
AHC, Kenosha	125 (9.3)	70	88	9	63	44.1 (12.0)	5.3 (2.1)	20.1 (7.8)
AHC, Racine	91 (6.8)	47	79	17	74	43.9 (11.1)	5.4 (2.0)	20.2 (7.0)
AHC, Hartford	118 (8.8)	59	99	1	80	42.5 (11.9)	5.2 (2.1)	20.9 (9.1)
AHC–Family Practice, Oshkosh	79 (5.9)	56	98	0	63	44.6 (12.9)	4.8 (2.3)	20.0 (9.2)
AHC–Internal Medicine, Oshkosh	50 (3.7)	50	100	0	50	52.8 (12.2)	5.7 (2.1)	23.3 (11.5)
AHC, Slinger	69 (5.1)	65	97	1	68	45.9 (11.7)	4.9 (2.1)	19.7 (8.1)

Abbreviations: CPD, cigarettes per day; FTND, Fagerström test for nicotine dependence.²⁵

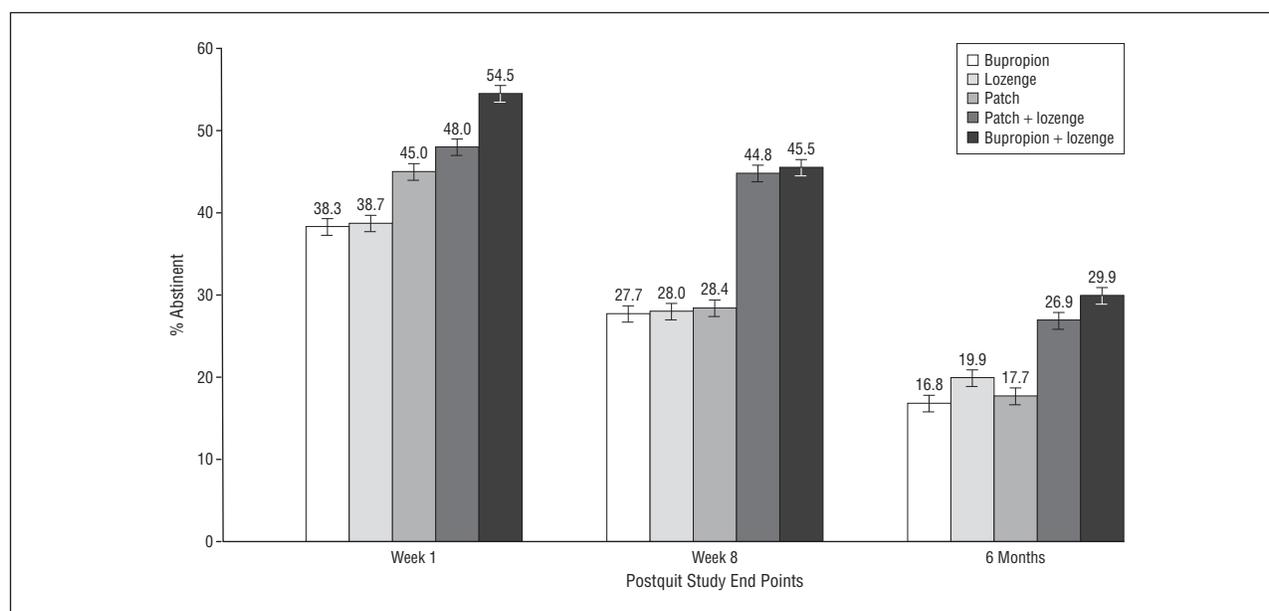


Figure 2. Abstinence rates at postquit study end points. Bupropion was administered as bupropion hydrochloride sustained release. Error bars indicate SE.

broad range of patient ethnicity, smoking heaviness, employment status, and other characteristics. There were statistically significant clinic differences, as expected given the diversity of patient populations served by the clinics, for all variables ($P \leq .001$) in Table 2 except for the Fagerström Test for Nicotine Dependence score.²⁵

ANALYSES OF PRIMARY ABSTINENCE OUTCOMES

Figure 2 provides 7-day point prevalence abstinence rates by treatment group at the 3 postquit study end points. Consistent with study hypotheses, preliminary analyses (with no correction for multiple tests) showed no differences among the 3 monotherapies, or between the 2 combination therapies, at any of the study end points. Thus, subsequent analyses compared each combination therapy with each of the monotherapies as planned. **Table 3** provides results for multivariate logistic regression analyses that tested the hypothesis that combination therapies would be supe-

rior to monotherapies. As given in Table 3, with Bonferroni correction, only 2 combination vs monotherapy comparisons were significant at 1 week; all Bonferroni-corrected comparisons were statistically significant at 8 weeks; and all comparisons except one (patch + lozenge vs lozenge) were significant at 6 months. Adjusted ORs for statistically significant (Bonferroni-corrected) comparisons ranged from 0.51 to 0.67 at 1 week, from 0.44 to 0.47 at 8 weeks, and from 0.46 to 0.56 at 6 months. Without correction for multiple tests, all comparisons (of combination vs monotherapies) for all 3 end points were statistically significant except for patch + lozenge vs patch at 1 week ($P = .48$) and patch + lozenge vs lozenge at 6 months ($P = .06$).

A total of 1027 cases (76.3% of the total sample) had smoking calendar data available for Cox regression survival analyses. The percentage of missing cases did not differ across the 5 treatment groups ($\chi^2 [N = 1346] = 3.83$; $P = .43$). Mean days to relapse, Wald values, P values, and ORs are provided in **Table 4**. Both combination thera-

Table 3. Combination Cessation Pharmacotherapy vs Monotherapy Group Comparisons at Study End Points; Point Prevalence Abstinence

Comparison ^a	1 Week After Quitting			8 Weeks After Quitting			6 Months After Quitting		
	Abstinence Rate, %	OR (95% CI)	P Value	Abstinence Rate, %	OR (95% CI)	P Value	Abstinence Rate, %	OR (95% CI)	P Value
Bupropion ^b + lozenge vs:	54.5	1 [Reference]		45.5	1 [Reference]		29.9	1 [Reference]	
Bupropion ^b only	38.3	0.51 (0.36-0.73)	<.001 ^c	27.7	0.44 (0.30-0.64)	<.001 ^c	16.8	0.46 (0.30-0.70)	<.001 ^c
Nicotine lozenge	38.7	0.51 (0.36-0.73)	<.001 ^c	28.0	0.45 (0.31-0.65)	<.001 ^c	19.9	0.56 (0.37-0.84)	.005 ^c
Nicotine patch	45.0	0.68 (0.48-0.96)	.03	28.4	0.45 (0.31-0.64)	<.001 ^c	17.7	0.48 (0.31-0.72)	<.001 ^c
Patch + lozenge vs:	48.0	1 [Reference]		44.8	1 [Reference]		26.9	1 [Reference]	
Bupropion ^b only	38.3	0.66 (0.46-0.94)	.02	27.7	0.45 (0.31-0.65)	<.001 ^c	16.8	0.54 (0.35-0.82)	.004 ^c
Nicotine lozenge	38.7	0.67 (0.47-0.96)	.03	28.0	0.47 (0.33-0.68)	<.001 ^c	19.9	0.67 (0.45-1.01)	.06
Nicotine patch	45.0	0.89 (0.63-1.24)	.48	28.4	0.47 (0.33-0.68)	<.001 ^c	17.7	0.56 (0.37-0.85)	.006 ^c

Abbreviations: CI, confidence interval; OR, odds ratio.

^aFrom multivariate logistic regression analyses with treatment, clinic, sex, and race (white/nonwhite) as fixed effects.

^bBupropion was administered as bupropion hydrochloride sustained release.

^cStatistically significant based on Bonferroni-corrected *P* value of .008.

Table 4. Cox Regression Survival Analysis of Days to Relapse for Combination Cessation Pharmacotherapy vs Monotherapy

Comparison ^a (Group Size)	Nonmissing Cases, No. (%)	Days to Relapse, Mean (SD)	Odds Ratio ^b (95% Confidence Interval)	P Value
Model 1				
Bupropion ^c + lozenge vs:	208 (78)	82.7 (87.8)	1 [Reference]	
Bupropion ^c only	186 (73)	49.1 (70.4)	1.54 (1.23-1.92)	<.001 ^d
Nicotine lozenge only	199 (76)	59.3 (77.0)	1.39 (1.11-1.73)	.004 ^d
Nicotine patch only	224 (79)	58.7 (79.9)	1.36 (1.10-1.69)	.005 ^d
Model 2				
Patch + lozenge vs:	210 (75)	82.4 (84.9)	1 [Reference]	
Bupropion ^c only	186 (73)	49.1 (70.4)	1.54 (1.23-1.93)	<.001 ^d
Nicotine lozenge only	199 (76)	59.3 (77.0)	1.36 (1.09-1.69)	.007 ^d
Nicotine patch only	224 (79)	58.7 (79.9)	1.34 (1.08-1.66)	.008 ^d

^aTested in 2 separate Cox regression models; model 1 tested bupropion + lozenge vs each monotherapy (bupropion, lozenge, and patch); model 2 tested patch + lozenge vs each monotherapy.

^bAdjusted for clinic, sex, and race (white/nonwhite).

^cBupropion was administered as bupropion hydrochloride sustained release.

^dStatistically significant based on Bonferroni-corrected *P* value of .008.

pies resulted in lower risk of relapse compared with each of the 3 monotherapies (Bonferroni-corrected *P* values). **Figure 3** provides survival curves for the 3 monotherapies and 2 combination therapies.

WTQL USE AND CESSATION OUTCOME

Among the 1346 study participants, a total of 545 participants (40.5%) completed at least 1 WTQL counseling call. There were no statistically significant differences across the 5 treatment groups in use of the WTQL (χ^2 [N=1346]=9.34; *P*=.053). Utilization rates in the 5 treatment groups were 35.5% for bupropion, 44.4% for lozenge, 38.7% for patch, 46.3% for bupropion SR + lozenge, and 37.6% for patch + lozenge. Users of the WTQL did not differ from nonusers in nicotine dependence (Fagerström Test for Nicotine Dependence mean for both groups was 5.1), sex, or race, but WTQL users were significantly older (mean, 45.3 years) than nonusers (mean 43.7 years) (*P*=.01).

To examine the association between WTQL use and cessation outcome, we first computed 6-month abstinence rates in groups of quit line users defined by deciles

(10 groups) of the total minutes of telephone counseling. These results showed that there was not a linear increase in abstinence rates with more minutes of counseling but, instead, users with fewer than 90 minutes of counseling (*n*=316) had an abstinence rate of 19.6% that was nearly the same as the rate for nonusers of the WTQL (*n*=801; abstinence rate, 19.5%). In contrast, WTQL users who had more than 90 minutes of counseling had a 6-month abstinence rate of 35.8% (*P*<.001).

COMMENT

In this comparative effectiveness study, we found that combination pharmacotherapies for smoking cessation were superior to the 3 monotherapies, especially at 8 weeks and 6 months. Bupropion SR + lozenge combination therapy was especially effective relative to the monotherapies with an approximate doubling of abstinence rates at 8 weeks and 6 months. Similar, though less consistent, results were found for the patch + lozenge combination condition. Survival analyses of risk of relapse yielded similar results. These results generally accord well with the findings from the

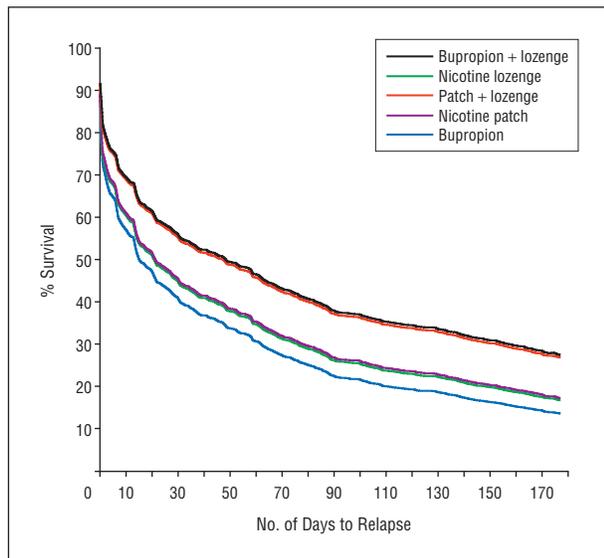


Figure 3. Cox regression survival analysis: survival curves. Bupropion was administered as bupropion hydrochloride sustained release.

separate RCT efficacy study²⁰ that tested the same 5 pharmacotherapy treatments. Biochemically confirmed 6-month point prevalence abstinence rates in the efficacy study were 31.8% for bupropion, 33.5% for lozenge, 33.5% for patch, 33.2% for bupropion SR + lozenge, and 40.1% for patch + lozenge.²⁰ In particular, both studies found that the patch + lozenge combination therapy was superior to the monotherapies but, unlike the efficacy RCT study, the present effectiveness study also found that the bupropion SR + lozenge combination therapy was superior to the monotherapies. Taken together, these 2 studies provide independent evidence, consistent with the 2000 and 2008 PHS Guidelines,^{4,15} that combination cessation pharmacotherapy results in significantly higher long-term abstinence rates compared with cessation monotherapies.

The present study expands on earlier research⁷ in demonstrating that a substantial proportion of primary care smokers attending routine clinic appointments were willing to make a cessation attempt. Among 7128 eligible smokers, 2677 (37.6%) were interested in study participation; 2371 (33.3%) passed medical screening; and 1346 (18.9%) consented to participation, were randomized to treatment, and picked up study medications. Thus, approximately 1 in 5 primary care patients smoking 10 or more CPD were willing to undertake an unplanned quit attempt during a primary care visit that included the opportunity to receive free medication and telephone cessation counseling.

The present study is limited to some extent by the fact that self-reported abstinence was not biochemically confirmed. As such, abstinence rates based on self-report could be overestimates. However, there is evidence that self-reported abstinence rates are generally accurate in low-contact effectiveness studies.^{22,26,27} It is worth noting that the majority of study participants did not use quit line counseling, but it is unknown to what extent this lack of broader quit line use may have resulted in lower abstinence rates. However, epidemiologic research using 2003 Current Population Survey data on 29 537 US smok-

ers has shown a very low rate (4.1%) of use of counseling (individual, group, and telephone) among smokers making quit attempts.²⁸ Thus, the use of the quit line for counseling by approximately 40% of participants in the present study is encouraging.

The tobacco cessation intervention model used in this study is consistent with recommendations in the 2008 PHS Guideline⁴ concerning the use of cessation medications, quit lines, and more intensive counseling. The results confirmed that provision of free medication and easy access to counseling (via a telephone quit line), with both arranged in the primary care setting during a routine (non-cessation-related) appointment, can result in a relatively high level of unplanned quit attempts and good cessation success, especially with combination therapy (27% to 30% of patients were abstinent at 6 months). Assuming that 1 in 5 smokers visiting a primary care clinic for routine care will undertake an unplanned quit attempt and that up to 30 of every 100 of these smokers making a quit attempt could achieve long-term (6-month) cessation, the overall success (defined as long-term abstinence) of this intervention model corresponds to approximately 6 of every 100 primary care-based smokers (ie, all smokers including those not motivated to make a quit attempt) achieving long-term abstinence. As such, this model holds significant promise for assisting large numbers of smokers to quit given that tens of millions of smokers are seen each year in the primary care setting.

Additional research is needed on the cost-effectiveness of the interventions in the present study as well as potential future enhancements to this intervention delivery model (eg, how PCPs can increase smoker motivation to make a quit attempt). However, this comparative effectiveness study identified 2 particularly effective combination therapies for smoking cessation. These findings provide strong support for the wide-scale implementation of this efficient primary care-based intervention model that significantly reduces barriers to patient access to evidence-based cessation treatments.

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