Comparative Effectiveness of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics

Stevens S. Smith, PhD; Danielle E. McCarthy, PhD; Sandra J. Japuntich, PhD; Bruce Christiansen, PhD; Megan E. Piper, PhD; Douglas E. Jorenby, PhD; David L. Fraser, MS; Michael C. Fiore, MD, MPH; Timothy B. Baker, PhD; Thomas C. Jackson, MD

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.

Trial Registration: clinicaltrials.gov Identifier: NCT00296647

Arch Intern Med. 2009;169(22):2148-2155

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 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 Update⁴ (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 combination therapies (eg, bupropion hydrochloride sustained release [SR] + nicotine patch). Yet, most data on cessation pharmacotherapies come from placebo-controlled efficacy trials conducted under ideal circumstances (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.⁵

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. 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. 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 update9 and has been shown to increase the likelihood of successful quitting.10 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 trials16,17 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
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 1304 patients provided provisional consent to participate in the study and were randomized to a medication condition. Of these 1304 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 Guideline 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 method; 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
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 Verification 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 and relevant effectiveness studies 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).

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, 13,466 (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 1. Descriptive Statistics for Sociodemographic and Smoking History Variables for the Total Sample and by Treatment Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample (N=1346)</th>
<th>Bupropiona (n=256)</th>
<th>Nicotine Lozenge (n=261)</th>
<th>Nicotine Patch + Lozenge (n=282)</th>
<th>Bupropionb + Lozenge (n=288)</th>
<th>Nicotine Patch + Lozenge (n=279)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>44.3 (12.1)</td>
<td>44.0 (11.6)</td>
<td>42.9 (11.7)</td>
<td>44.5 (12.4)</td>
<td>45.4 (12.2)</td>
<td>44.8 (12.4)</td>
<td>.17</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>753 (56)</td>
<td>143 (56)</td>
<td>142 (54)</td>
<td>158 (56)</td>
<td>152 (57)</td>
<td>158 (57)</td>
<td>.99</td>
</tr>
<tr>
<td>Married</td>
<td>54</td>
<td>53</td>
<td>50</td>
<td>57</td>
<td>55</td>
<td>55</td>
<td>.60</td>
</tr>
<tr>
<td>Employed</td>
<td>72</td>
<td>72</td>
<td>76</td>
<td>69</td>
<td>73</td>
<td>73</td>
<td>.59</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>87</td>
<td>88</td>
<td>87</td>
<td>86</td>
<td>88</td>
<td>88</td>
<td>.13</td>
</tr>
<tr>
<td>African American</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>.92</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>.42</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>.17</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not a high school graduate</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>12</td>
<td>10</td>
<td>.13</td>
</tr>
<tr>
<td>High school graduate</td>
<td>44</td>
<td>48</td>
<td>49</td>
<td>38</td>
<td>44</td>
<td>43</td>
<td>.17</td>
</tr>
<tr>
<td>More than high school</td>
<td>33</td>
<td>39</td>
<td>38</td>
<td>47</td>
<td>44</td>
<td>47</td>
<td>.17</td>
</tr>
<tr>
<td>Age at first cigarette, mean (SD), y</td>
<td>14.4 (3.9)</td>
<td>14.5 (4.4)</td>
<td>14.3 (3.5)</td>
<td>13.9 (4.1)</td>
<td>14.4 (3.8)</td>
<td>14.8 (3.7)</td>
<td>.10</td>
</tr>
<tr>
<td>Cigarettes smoked per day, mean (SD), No.</td>
<td>20.3 (8.8)</td>
<td>20.4 (8.7)</td>
<td>19.9 (9.4)</td>
<td>19.9 (8.5)</td>
<td>20.7 (8.3)</td>
<td>20.4 (8.8)</td>
<td>.79</td>
</tr>
<tr>
<td>FTND score, mean (SD)</td>
<td>5.1 (2.1)</td>
<td>5.0 (2.1)</td>
<td>5.0 (2.2)</td>
<td>5.3 (2.1)</td>
<td>5.2 (2.0)</td>
<td>5.0 (2.1)</td>
<td>.43</td>
</tr>
<tr>
<td>Previous quit attempts, mean (SD), No.</td>
<td>5.7 (9.3)</td>
<td>5.9 (10.5)</td>
<td>5.3 (6.7)</td>
<td>5.5 (8.3)</td>
<td>5.4 (9.9)</td>
<td>6.3 (10.7)</td>
<td>.67</td>
</tr>
</tbody>
</table>

Abbreviation: FTND, Fagerström test for nicotine dependence.  
Bupropiona was administered as bupropion hydrochloride sustained release.

---

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, 13,466 (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...
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 ($P < .001$) 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 superior 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-
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 (χ²[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 (Fagerstrom 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

---

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

<table>
<thead>
<tr>
<th>Comparisona</th>
<th>1 Week After Quitting</th>
<th>8 Weeks After Quitting</th>
<th>6 Months After Quitting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstinence Rate, %</td>
<td>OR (95% CI) Value</td>
<td>Abstinence Rate, %</td>
</tr>
<tr>
<td>Bupropionb + lozengex vs:</td>
<td>54.5 [Reference]</td>
<td>.001c</td>
<td>45.5 [Reference]</td>
</tr>
<tr>
<td>Bupropionb only</td>
<td>38.3 (0.36-0.73)</td>
<td>.001c</td>
<td>27.7 (0.30-0.64)</td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>38.7 (0.36-0.73)</td>
<td>.001c</td>
<td>28.0 (0.31-0.65)</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>45.0 (0.48-0.96)</td>
<td>.001c</td>
<td>28.4 (0.31-0.64)</td>
</tr>
<tr>
<td>Patch + lozengex vs:</td>
<td>48.0 [Reference]</td>
<td>.001c</td>
<td>44.8 [Reference]</td>
</tr>
<tr>
<td>Bupropionb only</td>
<td>38.3 (0.46-0.94)</td>
<td>.001c</td>
<td>27.7 (0.31-0.65)</td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>38.7 (0.47-0.96)</td>
<td>.001c</td>
<td>28.0 (0.33-0.68)</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>45.0 (0.63-1.24)</td>
<td>.001c</td>
<td>28.4 (0.33-0.68)</td>
</tr>
</tbody>
</table>

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 .001.
dStatistically significant based on Bonferroni-corrected P value of .001.

---

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

<table>
<thead>
<tr>
<th>Comparisona</th>
<th>Group Size</th>
<th>Nonmissing Cases, No. (%)</th>
<th>Days to Relapse, Mean (SD)</th>
<th>Odds Ratiob (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropionb + lozengex vs:</td>
<td>208 (78)</td>
<td>82.7 (87.8)</td>
<td>1 [Reference]</td>
<td>&lt;.001d</td>
<td></td>
</tr>
<tr>
<td>Bupropionb only</td>
<td>186 (73)</td>
<td>49.1 (70.4)</td>
<td>1.34 (1.23-1.92)</td>
<td>.001d</td>
<td></td>
</tr>
<tr>
<td>Nicotine lozenge only</td>
<td>199 (76)</td>
<td>59.3 (77.0)</td>
<td>1.39 (1.10-1.73)</td>
<td>.004d</td>
<td></td>
</tr>
<tr>
<td>Nicotine patch only</td>
<td>224 (79)</td>
<td>58.7 (79.9)</td>
<td>1.36 (1.10-1.69)</td>
<td>.005d</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch + lozengex vs:</td>
<td>210 (75)</td>
<td>82.4 (84.9)</td>
<td>1 [Reference]</td>
<td>&lt;.001d</td>
<td></td>
</tr>
<tr>
<td>Bupropionb only</td>
<td>186 (73)</td>
<td>49.1 (70.4)</td>
<td>1.36 (1.23-1.93)</td>
<td>&lt;.001d</td>
<td></td>
</tr>
<tr>
<td>Nicotine lozenge only</td>
<td>199 (76)</td>
<td>59.3 (77.0)</td>
<td>1.36 (1.09-1.69)</td>
<td>.007d</td>
<td></td>
</tr>
<tr>
<td>Nicotine patch only</td>
<td>224 (79)</td>
<td>58.7 (79.9)</td>
<td>1.34 (1.08-1.66)</td>
<td>.008d</td>
<td></td>
</tr>
</tbody>
</table>

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 .001.
The present study expands on earlier research\(^7\) 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 smokers attending routine clinic appointments for routine care indicated that a substantial proportion of primary care 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 (i.e., 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 (e.g., 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.

Accepted for Publication: August 15, 2009.

Correspondence: Stevens S. Smith, PhD, University of Wisconsin Center for Tobacco Research and Intervention, 1930 Monroe St, Ste 200, Madison, WI 53711 (sss@ctri.medicine.wisc.edu).

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Smith, McCarthy, Japuntich, Christiansen, Piper, Jorenby, Fraser, Baker, and Jackson. Acquisition of data: Japuntich, Christiansen, Jorenby, Fraser, Baker, and Jackson. Analysis and interpretation of data: Smith, McCarthy, Piper, Fraser, Baker, and Jackson. Drafting of the manuscript: Smith, McCarthy, Japuntich, Christiansen, Piper, Jorenby, Baker, and Jackson. Administrative, technical, and material support: McCarthy, Japuntich, Christiansen, Piper, Jorenby, Fraser, Baker, and Jackson. Statistical analysis: Smith, McCarthy, Piper, and Baker. Obtained funding: Smith, McCarthy, Piper, Jorenby, Fraser, Baker, and Jackson. Study supervision: Smith, Fraser, Baker, and Jackson.

\(©2009\) American Medical Association. All rights reserved.

Figure 3. Cox regression survival analysis: survival curves. Bupropion was administered as bupropion hydrochloride sustained release.
Financial Disclosure: Dr Smith has received research support from Elan Corporation plc. Dr Jorenby has received research support from Pfizer Inc, Sanofi-Synthelabo, and Nabi Biopharmaceuticals and has received consulting fees from Nabi Biopharmaceuticals. Dr Fiore has received honoraria from Pfizer Inc and has served as an investigator on research studies at the University of Wisconsin that were funded by Pfizer Inc, Sanofi-Synthelabo, and Nabi Biopharmaceuticals. In 1998, the University of Wisconsin (UW) appointed Dr Fiore to a named Chair funded by an unrestricted gift to UW from Glaxo Wellcome. Dr Baker has served as an investigator on research projects sponsored by pharmaceutical companies including Sanofi-Synthelabo, Pfizer Inc, and Nabi Biopharmaceuticals.

Funding/Support: This research was supported by National Institutes of Health grant 5P50DA019706 (Dr Baker) from the National Institute on Drug Abuse and grant 1K05CA139871 (Dr Baker) from the National Cancer Institute. Dr Piper was supported by an Institutional Clinical and Translational Science Award (UW-Madison; KL2 grant 1KL2RR025012-01). Medication was provided to patients at no cost under a research agreement with GlaxoSmithKline.

Role of the Sponsors: No part of this manuscript was written or edited by anyone employed by GlaxoSmithKline.

Additional Contributions: We would like to acknowledge the contributions of the following organizations and individuals: the Aurora Health Care System; Aurora clinic physicians, medical assistants, and other clinic staff; counselors at the Wisconsin Tobacco Quit Line; staff at Free and Clear, Inc, Seattle, Washington; and research staff at the Milwaukee office of the University of Wisconsin Center for Tobacco Research and Intervention (Patti Weston, Sarah Cunitz, Meg Feyen, Leigh Ann Laczkowski, and Michelle Spehr).

REFERENCES

5. Conroy MB, Majchrzak NE, Regan S, Silverman CB, Schneider LJ, Rigotti NA. The association between patient-reported receipt of tobacco intervention at a primary care visit and smokers’ satisfaction with their health care Nicotine Tob Res. 2005;7(suppl 1):S29-S34.