

# Randomized Clinical Trial of the Efficacy of Bupropion Combined With Nicotine Patch in the Treatment of Adolescent Smokers

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Adolescent smokers ( $N = 211$ ) were randomized to 1 of 2 groups: (a) nicotine patch plus bupropion SR (sustained release; 150 mg per day) or (b) nicotine patch plus placebo. Group skills training sessions were conducted each week by research staff. Abstinence rates at Weeks 10 and 26 were as follows: (a) patch plus bupropion, 23% and 8%, (b) patch plus placebo, 28% and 7%. Despite the lack of a treatment effect, a large majority of adolescents in both treatment groups reduced their consumption to a few cigarettes per day or less and maintained this reduction over time. Similarly, an examination of survival curves revealed that by the end of treatment many had managed to avoid a return to daily smoking. These findings are encouraging and suggest new avenues for research. For example, treatments of the kind examined in this report, augmented by extended maintenance therapies, may yield higher long-term success rates.

Cigarette smoking during adolescence remains an alarming public health problem. About 7%, 14%, and 21% of 8th, 10th, and 12th graders in the 2000 *Monitoring the Future* survey reported daily smoking (Johnston, O'Malley, & Bachman, 2000). These rates are substantial and would be even higher if high school dropouts were included in study samples.

Such findings have led to calls for the development of effective cessation programs for adolescent smokers. However, few controlled cessation trials for adolescents have been conducted, and the lack of promising approaches is a recognized problem (Sussman, Lichtman, Ritt, & Pallonen, 1999).

Nicotine replacement therapy is now considered the state-of-the-art treatment for adults smokers. Two open label studies have examined nicotine patch treatment (NP) for adolescent smokers. In the first report (Smith et al., 1996), 14% were smoke free at the end of treatment, with 5% remaining smoke free at 6-month follow-up. In the second study, point prevalence abstinence was 11% at 6 weeks and 5% at 26 weeks (Hurt et al., 2000).

Bupropion hydrochloride, an aminoketone antidepressant, is also approved as an adjunct in smoking cessation therapy. Several

placebo-controlled efficacy trials with adult smokers have been published. In the first trial, 6-month abstinence rates were 16% for placebo and 27% for bupropion (150 mg and 300 mg; Hurt et al., 1997). In a second trial, 6-month abstinence rates were 25% for bupropion and 16% for placebo (Hall et al., 2002).

In the only trial to our knowledge to examine bupropion in combination with NP, 6-month abstinence rates were as follows: placebo, 19%; NP, 21%; bupropion, 35%; bupropion + NP, 39% (Jorenby et al., 1999). Only the bupropion-treatment groups were significantly different from placebo.

This article presents results of a smoking cessation trial designed to examine the efficacy of a treatment for adolescent smokers that combines NP with bupropion. The trial addressed several important gaps in our knowledge of effective smoking cessation treatment. First, it is perhaps the first randomized controlled trial of pharmacotherapy for adolescent smoking cessation and one of a very few randomized smoking cessation trials for adolescents yet conducted. Second, it is to our knowledge the first study with adolescent smokers to examine the efficacy of a treatment combining nicotine replacement therapy with antidepressant medication. Third, it is one of the first smoking cessation trials with adolescents to combine relapse prevention skills training with pharmacotherapy.

## Method

### Design

A total of 211 smokers (age 15–18 years, 145 boys, 66 girls) were randomized to one of two treatment groups: (a) NP + placebo or (b) NP + bupropion SR (150 mg). All received group-based skills training. Participants received \$50 for completing the end of treatment assessment (Week 10) and \$50 for completing a 26-week assessment. Assignment to treatment condition was double blind. Parental consent was required for participation. The protocol was approved by the Stanford University panel for the protection of human subjects in medical research.

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### Recruitment of Participants

Adolescent smokers were recruited over a period of 2.5 years from nine continuation high schools in the San Francisco Bay area. Potential participants received a comprehensive history and physical exam conducted by a study physician and an assessment of past and current depression and current drug use.

To be randomized, adolescents had to report that they (a) currently smoked at least 10 cigarettes per day, (b) had smoked for at least 6 months, (c) had made one or more failed attempts to quit smoking, and (d) scored 10 or more on a modified version of the Fagerström Tolerance Questionnaire (mFTQ; Rojas, Killen, Haydel, & Robinson, 1998). These entry criteria were chosen following discussions with the Food and Drug Administration in conjunction with the requirement that the study be conducted under Investigational New Drug Application approval.

### Measures

The measurement schedule for this trial is presented in Table 1. In addition to basic demographics, smoking history, and medical status, the following measures were obtained during the trial.

*Screen for current major depression (MDD).* MDD was diagnosed with the mood disorders portion of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders* (First, Spitzer, Gibbon, & Williams, 1996). Those meeting criteria for current MDD were excluded from the study.

*mFTQ.* Nicotine dependence was assessed with the mFTQ.

*Craving.* Craving was measured with two items (see Killen & Fortmann, 1997).

*Depression symptoms.* Depression symptoms were measured with the Center for Epidemiological Studies depression instrument (CES-D; Radloff, 1977).

*Blood pressure and heart rate.* Blood pressure and heart rate were measured three times at each session with an automated blood pressure device (DINAMAP XL 9300; Johnson & Johnson Medical, New Brunswick, New Jersey).

*Bupropion metabolite assay.* Urine samples were obtained from all participants at Week 5 and analyzed for the presence of bupropion and its hydroxylated metabolite.

*Self-reported compliance.* At all sessions participants reported on their patch and pill use in the previous week.

Table 1  
Schedule of Measurements

Measurement	Baseline	Weekly	Week 10	Week 26
Blood pressure	×	×	×	
Heart rate	×	×	×	
mFTQ	×			
Craving	×	×	×	
Amount smoked	×	×	×	×
SCID	×		×	
CES-D	×	× <sup>a</sup>	×	
Saliva cotinine				×
Expired-air CO	×	×	×	×
Adverse events		×		

*Note.* mFTQ = modified Fagerström Tolerance Questionnaire; SCID = Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*; CES-D = Center for Epidemiological Studies depression instrument; CO = carbon monoxide.

<sup>a</sup> CES-D was obtained in Weeks 1, 2, 3, 4, 10; urine for metabolite determination was obtained in Week 5.

*Expired-air carbon monoxide (CO)–salivary cotinine.* Nonsmoking status was assessed at all sessions by examination of expired-air carbon monoxide and by saliva cotinine concentration at Week 26.

Abstinence at end of treatment was defined as a report of nonsmoking (not even a puff) for 7 consecutive days prior to contact and a carbon monoxide level below 9 ppm. Abstinence at Week 26 was defined as a report of nonsmoking (not even a puff) for 7 consecutive days prior to contact and a saliva cotinine level below 20 ng/ml.

Except for participants who were outside the area at the time of assessment, all those who reported abstinence but who failed to provide breath or saliva samples for the relevant biochemical confirmation were classified as smokers.

### Treatments

*Quit date.* Participants were required to quit smoking 2 weeks after the first group counseling session. The quit date was defined as the date on which a participant was able to quit smoking cigarettes for a 24-hr period.

*Nicotine patch.* All participants received treatment with NP for 8 weeks. On the basis of amount smoked, we assigned participants to appropriate patch regimen. If they smoked more than 15 cigarettes per day, they wore 21-mg patches during Weeks 1–4, 14-mg patches in Weeks 5–6, and 7-mg patches in Weeks 7–8. However, if participants smoked between 10 and 15 cigarettes per day, they wore 14-mg patches in Weeks 1–6, and 7-mg patches in Weeks 7–8.

*Bupropion.* Participants were randomized to receive bupropion SR (150 mg per day) or matching placebo. The medication was taken for 9 weeks starting after the first group skills training session 1 week prior to the quit date.

*Group skills training.* Participants met weekly in groups (average group size = 8) supervised by trained counselors. In each 45 min session, counselors (a) demonstrated the use of specific, concrete self-regulatory skills for coping with risky situations without resorting to smoking, (b) provided participants with an opportunity to rehearse modeled skills, and (c) helped participants develop action plans designed to promote nonsmoking in self-identified, high-risk situations.

## Results

### Results of Initial Screening

A total of 226 adolescent smokers met eligibility criteria out of 543 screened. A total of 211 were randomized. Randomization produced treatment groups that were similar on all baseline variables (see Table 2).

Of those not randomized, 219 were not eligible, 55 failed to complete screening, 22 were not interested, and 21 could not participate for a variety of other reasons. Reasons for exclusion are presented in Table 3.

### Reclassification

Of self-reported nonsmokers, 95% and 34% provided biochemical confirmation in Weeks 10 and 26, respectively. Those failing to provide confirmation were reclassified as smokers except for 1 participant who reported nonsmoking but was out of the area and unavailable for biochemical testing. Furthermore, at Week 10 we reclassified 3 participants who reported nonsmoking but had carbon monoxide levels greater than 9 ppm, and at Week 26 we reclassified 4 participants who exceeded the cotinine cutpoint. Finally, 20% of those who met self-report and biochemical criteria for nonsmoking at end of treatment could not be located at follow-up and were classified as smokers.

Table 2  
Baseline Variables

Variable	NP + placebo		NP + bupropion	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Cigarettes smoked per day	15.65	6.40	15.12	5.33
mFTQ	16.63	2.65	16.80	3.03
CES-D	14.14	9.56	14.23	9.34
Age (years)	17.32	0.80	17.32	0.73
History of MDD (%)		11		11
Gender (%)				
Male		69		69
Female		31		31
Race/ethnicity (%)				
White	54.63		45.63	
African American	2.78		1.94	
Hispanic/Latino	11.11		13.59	
Native American	0.00		1.94	
Pacific Islander/Filipino	3.70		8.74	
Asian	7.41		6.80	
Multiethnicities	17.59		21.36	
Unknown	2.78		0.00	
<i>n</i>		108		103

Note. NP = nicotine patch treatment; mFTQ = modified Fagerström Tolerance Questionnaire; CES-D = Center for Epidemiological Studies depression instrument; MDD = major depression.

### Compliance to Treatment Protocols

**Session attendance.** Eighty percent of participants attended at least eight treatment sessions.

**Reported patch use.** About 29% of participants reported that they used all their patches on at least 5 treatment weeks. However, 41% reported that they used all their patches on only 2 treatment weeks or less.

Table 3  
Reasons for Exclusion From Trial

Reason	Number excluded
Daily drug use	11
Current depression	6
History of seizure disorder	7
Family history of seizures	25
History of concussion	39
Kidney disease	2
Congestive heart failure	1
Anorexia nervosa or bulimia	2
Reaction to Zyban or Wellbutrin	1
Allergy to adhesive tape	1
Current use of an antidepressant	16
Use of other exclusionary medication	9
Not enough cigarettes	65
Too old	6
Excluded for other reason (staff judgment)	13
Fagerström score too low	3
Not smoking long enough	1
Already quit	4
Parent or guardian refused consent	5
Breastfeeding	2
Total	219

**Urinalysis.** At Week 5, 38% of participants in the patch plus bupropion treatment condition (39 of 103) had measurable levels of bupropion in urine.

**Reported pill use.** Only 22% of participants said that they used all their pills on at least 6 treatment weeks, and 44% reported that they used all their pills on 2 treatment weeks or less.

### Response to Treatment: Analysis of Reports of Smoking Abstinence

Logistic regression analysis was used to test the main hypothesis that the combined treatment would produce higher abstinence rates at Weeks 10 and 26. Separate models were fit for each follow-up point using biochemically confirmed smoking status as the dependent variable and treatment group as the independent variable. We did not observe a main effect for treatment (see Table 4).

### Response to Treatment: Survival Analysis

This report represents to our knowledge the first examination of time-to-relapse data in adolescent smokers undergoing smoking-cessation therapy. Relapse curves were analyzed with survival analysis using the Cox proportional hazards model (Allison, 1995) with time to relapse as the dependent variable and treatment condition as the independent variable. The relapse date was defined as the first day that a participant smoked for 7 consecutive days. Groups did not differ in time to relapse (see Figure 1).

### Response to Treatment: Change in Amount Smoked per Day

The effect of treatment on cigarette consumption rates was examined with a random regression model. The log value of reported cigarettes smoked per day served as the dependent variable in the analysis. Treatment group, mFTQ score, time, and the interactions were included in the model. Cigarette consumption decreased significantly over the treatment interval,  $F(1, 53) = 472.67, p < .01$ , but no main or interaction effects were detected. The average number of cigarettes smoked per day at each time point and average regression line (average intercepts and slopes

Table 4  
Percentage Abstinent and Number Assessed by Time and Treatment Group

Treatment group	Week 10	Week 26
NP + placebo ( <i>n</i> = 108)		
% abstinent	28	7 (21)
No. assessed	94	70
NP + bupropion ( <i>n</i> = 103)		
% abstinent	23	8 (16)
No. assessed	83	64

Note. Numbers in parentheses represent the percentage of participants at Week 26 who were abstinent on the basis of self-report but who were missing cotinine values; at Week 10, all those who said that they were not smoking at end of treatment provided an expired-air sample. NP = nicotine patch treatment.

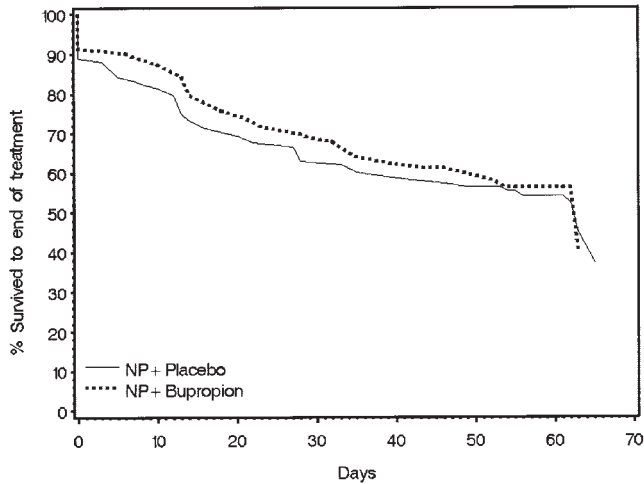


Figure 1. Survival analysis to end of treatment. NP = nicotine patch treatment.

from individual regression lines using all available data) are given in Figure 2.

*Response to Treatment: Compliance to Medication Protocols*

A logistic regression model was used to examine abstinence rates at end of treatment (Week 10) as a function of bupropion

metabolite level, patch use, and session attendance. Those who attended more treatment sessions,  $\chi^2(1, N = 211) = 3.83, p = .05$ , and reported using more nicotine patches,  $\chi^2(1, N = 211) = 3.51, p = .06$ , were more likely to be abstinent at end of treatment.

We also modeled amount smoked per day as a function of compliance to treatment protocols using random-regression methods. Those with a detectable level of the metabolite in Week 5,  $F(2, 315) = 5.72, p < .01$ , and those reporting more patch use,  $F(1, 282) = 6.85, p < .01$ , reported significantly lower levels of smoking during treatment. In contrast, attendance at sessions was not associated with reduced levels of smoking ( $p = .72$ ).

*Impact of Treatment on Craving*

The effect of treatment on craving was examined with a random-regression model. Only participants who were abstinent at end of treatment were included in this analysis. Treatment group, time, baseline mFTQ score, and the interactions were included in the model (see Figure 3). Craving decreased significantly over the treatment interval,  $F(1, 50) = 109.04, p < .01$ , but no main or interaction effects were detected. The average craving level at each time point and average regression line (average intercepts and slopes from individual regression lines using all available data) are given in Figure 3.

*Impact of Treatment on CES-D Score*

The effect of treatment on CES-D score was examined with a random-regression model. Treatment group, time, history of

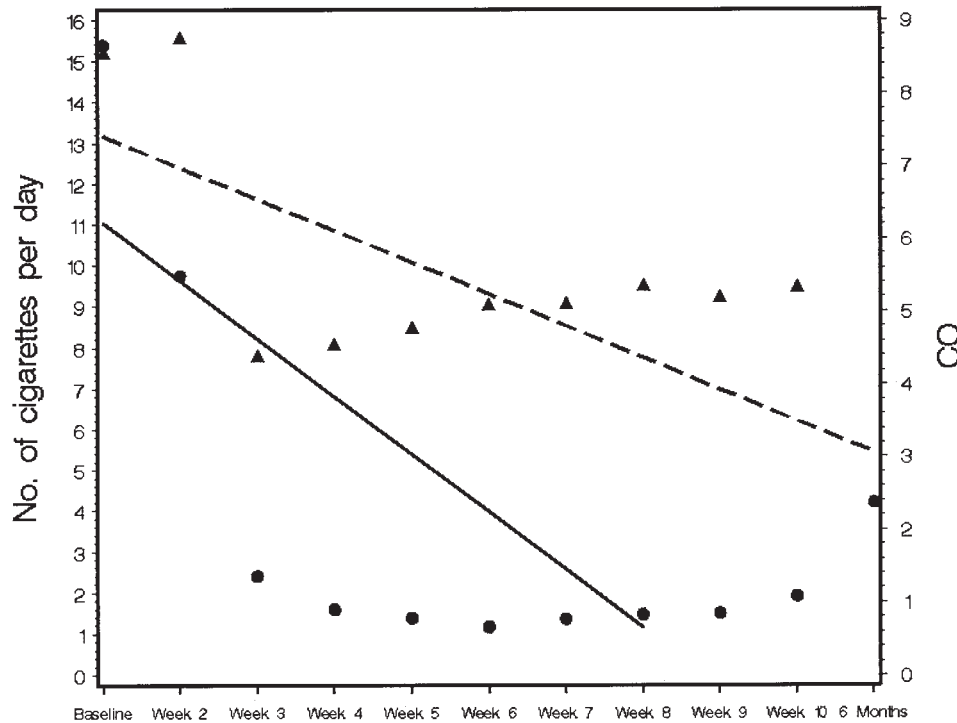


Figure 2. Average number of cigarettes per day versus average carbon monoxide (CO) over time and their average regression lines. Solid triangles = average CO; the dashed line = CO regression line; solid circles = average number of cigarettes per day; the solid line = cigarettes per day regression line.

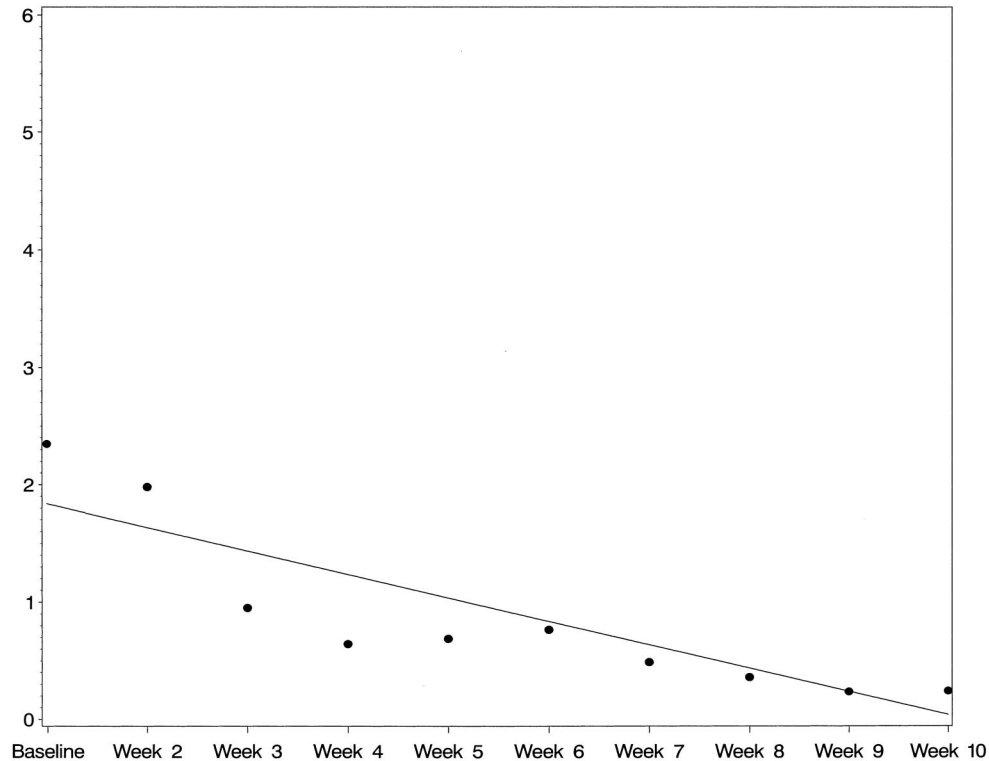


Figure 3. Average craving scores over time and average regression line. Solid circles = average craving scores.

MDD, and their interactions were included in the model. Depression symptoms decreased significantly over the treatment interval,  $F(1, 181) = 25.69, p < .01$ , but no main or interaction effects were detected. The average CES-D score at each time point and average regression line (average intercepts and slopes from individual regression lines using all available data) are given in Figure 4.

#### Adverse Events

Adverse events are presented in Table 5. A total of 47 complaints, 25 in the patch plus placebo treatment group and 22 in the patch plus bupropion treatment group, were rated as severe by participants and prompted follow-up from research staff. None of the adverse events were judged to be truly severe by the lead study physician.

Blood pressure (systolic/diastolic) and heart rate averaged across the 10 assessments were as follows: patch plus placebo = 117/62, 78; patch plus bupropion = 116/63, 78. Significant elevations in blood pressure were not observed.

#### Maintenance of the Blind

Participants were asked to guess their treatment assignment at Week 10. Only 30% (28 of 92) of those in the patch plus placebo condition and 31% (26 of 83) of those receiving patch plus bupropion guessed their assignment correctly.

#### Discussion

To our knowledge, only a handful of studies examining smoking cessation therapies for adolescents have been conducted. Very few

have used even minimal methodologic standards (Mermelstein et al., 2002; Sussman et al., 1999). Quit rates in these studies ranged from 6% to 15%. Thus, the results of this trial, although mixed, are of significant interest.

The addition of bupropion to NP did not improve abstinence rates. This finding is not consistent with the one published trial that examined the efficacy of this treatment combination in adult smokers (Jorenby et al., 1999). However, the abstinence rates achieved at end of treatment are similar to rates achieved by NP in studies conducted with adult smokers. Thus, for example, in one meta-analysis mean abstinence rates for NP users were 27% at end of treatment and 22% at 6 months compared with 13% and 9%, respectively, for placebo (Fiore, Smith, Jorenby, & Baker, 1994).

Although our end-of-treatment results are similar, adolescents in this study appear to return to smoking more precipitously than adults with abstinence rates at Week 26 that mirror those reported in other trials conducted with their peers (Sussman et al., 1999). The longer-term abstinence rates reported here may underestimate outcomes to a degree, however, because 20% of confirmed non-smokers at end of treatment and a large number of participants who had reduced consumption to a few cigarettes per week were lost to follow-up. Furthermore, 21 participants reported not smoking at follow-up but were unavailable for cotinine testing for a variety of reasons. Because our data suggest that participants were generally willing to report their smoking status accurately, we have also provided abstinence rates based on self-report only. This allows more direct comparison with the majority of published reports of adolescent smoking cessation treatment research.

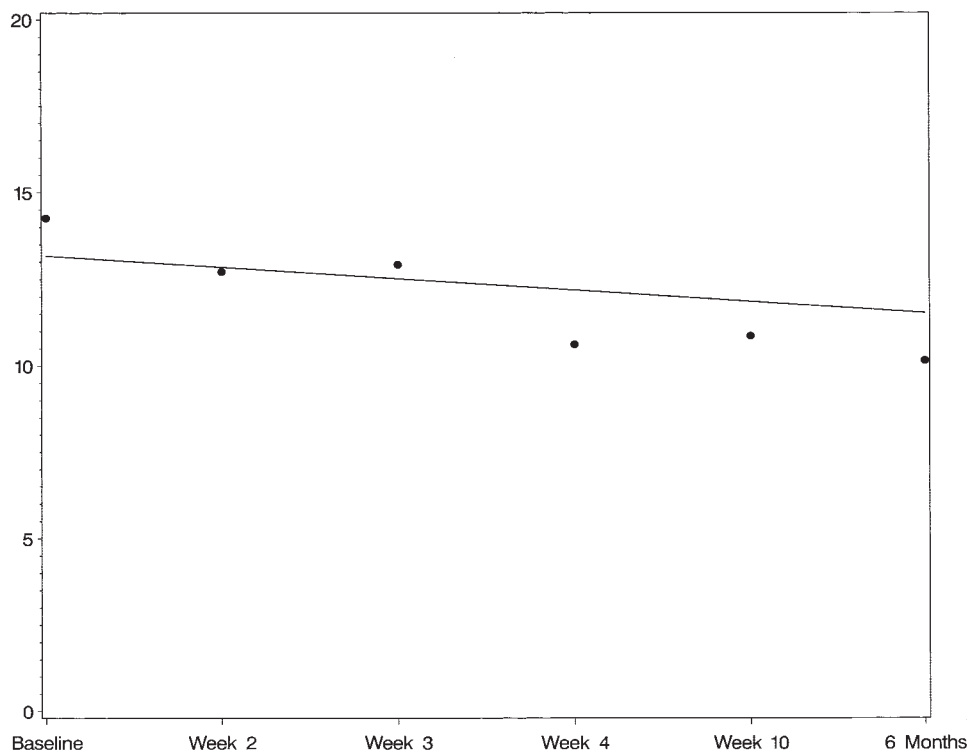


Figure 4. Average CES-D scores over time and average regression line. Solid circles = average CES-D scores. CES-D = Center for Epidemiological Studies depression instrument.

Perhaps bupropion failed to improve abstinence rates because the dosage used in this study was 150 mg per day. The recommended dosage for adult smokers is 300 mg per day. However, we chose to provide adolescent smokers with a reduced dose because pediatric samples were not included in the studies conducted to establish safety and efficacy. In addition, in the trial conducted by Hurt et al. (1997), point prevalence abstinence rates for 150-mg and 300-mg groups were significantly different from placebo at 6 months and 1 year but not different from each other (6 months: 150

mg = 27.5%; 300 mg = 26.9%; 12 months: 150 mg = 22.9%; 300 mg = 23.1%).

Abstinence rates in this study might also have been higher had participants followed treatment protocols more faithfully. Although most attended treatment sessions on a regular basis, compliance to medication protocols was low.

To place the compliance data in context, it is generally the case that compliance to medication and behavioral-treatment regimens is poor. Thus, in a review of over 70 outcome studies for hypertension, diabetes, and asthma, less than 50% of patients with diabetes complied with their medication schedule, and less than 30% of patients with hypertension or asthma complied with instructions (O'Brien & McLellan, 1996). In general, reports of compliance data in the smoking cessation literature are typically missing. When available, findings indicate substantial deviations from NP treatment protocols (Westman, Levin, & Rose, 1993). Comparisons with the literature on the use of bupropion for smoking cessation in adults are difficult because, with one exception (Hall et al., 2002), compliance data are not reported.

Little is known about the development of withdrawal symptoms among adolescent smokers. In this trial, craving scores and depression symptoms declined over the course of treatment but the addition of bupropion to NP conferred no additional therapeutic benefit. Most studies of nicotine gum have not shown effects on craving, and the results from trials with NP have been mixed. Similarly, the evidence that treatment with antidepressants actually alleviates depression symptoms associated with smoking cessation

Table 5  
Number of Participants Reporting Adverse Events

Adverse event	Severe		Moderate	
	NP + B (n = 103)	NP (n = 108)	NP + B (n = 103)	NP (n = 108)
Dimness of vision	1	1	0	0
Skin rash	1	0	3	4
Nausea	3	4	4	6
Confusion	1	0	0	1
Digestive problems	1	0	1	0
Agitation	0	0	1	1
Headache	1	0	2	1
Weakness	0	2	0	2
Sweating	0	1	0	0
Dizziness	2	1	1	3
Other	12	16	12	17

Note. NP = nicotine patch treatment; B = bupropion.

is rather sparse. For example, controlled investigations of bupropion generally have not found effects.

This is one of the first studies to examine the safety and adverse events profile of nicotine replacement therapy in the treatment of adolescent smokers. It is to our knowledge the first report of adverse events associated with the use of bupropion in treating adolescent smokers. The medications appeared to be safe and were well tolerated. Blood pressure and heart rate did not increase during treatment and did not differ significantly across treatment groups. Similarly, there was no significant difference in the number of adverse events rated as severe. In a recent review of methodological issues associated with the measurement of treatment outcome in adolescent smoking cessation studies, Mermelstein et al. (2002) emphasized that very little is known about the process by which adolescents alter their smoking habits. These authors argued that intermediate cessation outcomes such as reductions in consumption and survival (nonrelapse) rates should be examined in reports of adolescent smoking cessation research because an increased understanding of the patterns and processes of change may lead to the development of more effective treatments (Mermelstein et al., 2002).

Given this context, the impact of treatment on relapse as well as cigarette consumption among adolescent smokers in our study is of interest. As our data indicate, the large majority of adolescents in both treatment groups reduced their consumption to a few cigarettes per day or less. Expired-air carbon monoxide levels obtained throughout treatment confirm the veracity of self-reports. Similarly, an examination of survival curves reveals that by the end of treatment many had managed to avoid a return to daily smoking. Of note, medication use, as indexed by both metabolite analysis and self-report, appeared to significantly reduce cigarette consumption. This conclusion is strengthened because compliance, as measured by attendance at treatment sessions, was not associated with smoking reductions. These findings are encouraging and suggest new avenues for research. For example, treatments of the kind examined in this report, augmented by extended maintenance therapies, may yield a more durable treatment response.

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