ARTICLE

Randomized, Double-blind, Placebo-Controlled Trial of 2 Dosages of Sustained-Release Bupropion for Adolescent Smoking Cessation

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Objective: To assess the safety and efficacy of sustained-release bupropion hydrochloride for adolescent smoking cessation.

Design: Prospective, randomized, double-blind, placebo-controlled, dose-ranging trial.

Setting: Metropolitan areas of Tucson and Phoenix, Arizona.

Participants: Adolescents (N=312) recruited through media and various community venues from March 1, 1999, through December 31, 2002, who were aged 14 to 17 years, smoked 6 or more cigarettes per day, had an exhaled carbon monoxide level of 10 ppm or greater, had at least 2 previous quit attempts, and had no other current major psychiatric diagnosis.

Intervention: Sustained-release bupropion hydrochloride, 150 mg/d (n=105) or 300 mg/d (n=104), or placebo (n=103) for 6 weeks, plus weekly brief individual counseling. Subjects were followed up at 12 weeks (by telephone call) and 26 weeks.

Main Outcome Measure: Confirmed 7-day point prevalence abstinence at 6 weeks and 30-day prolonged abstinence (carbon monoxide level <10 ppm at each visit; urinary cotinine level ≤ 50 µg/L at weeks 2 and 6).

Results: Cotinine-confirmed 7-day point prevalence abstinence rates at 6 weeks were as follows: placebo, 5.6%; 150 mg, 10.7%; and 300 mg, 14.5% ($P=.03$, 300 mg vs placebo). At 26 weeks, confirmed point prevalence abstinence rates were as follows: placebo, 10.3%; 150 mg, 3.1%; and 300 mg, 13.9% ($P=.049$). During treatment, confirmed point prevalence rates were significantly higher for 300 mg than placebo at every week except week 4.

Conclusions: Sustained-release bupropion hydrochloride, 300 mg/d, plus brief counseling demonstrated short-term efficacy for adolescent smoking cessation. Abstinence rates were lower than those reported for adults, with rapid relapse after medication discontinuation.

Trial Registration: clinicaltrials.gov Identifier: NCT00344695

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SMOKING AMONG ADOLESCENTS remains a considerable public health challenge. An estimated 23.0% of high school students in the United States currently smoke cigarettes.[1] Most adult long-term smokers initiated smoking in adolescence, suggesting that many adolescent smokers will go on to become long-term smokers.[2,3]

Evidence suggests that adolescent smokers experience symptoms of tobacco dependence sooner after initiation and at lower levels of smoking than previously thought. One study found that 95% of adolescent smokers reported tobacco dependence symptoms when smoking fewer than 10 cigarettes per day.[4] Many youths are not able to quit smoking on their own. The 2000 National Youth Tobacco Survey found that, among current middle school smokers, 59.5% have tried to quit in the past 12 months and 55.0% want to quit.[5] Among current high school smokers, 59.3% have tried to quit in the past 12 months and 61.0% want to quit.[5] Other studies estimate that only about 4% of all adolescent smokers attempting to quit per year are successful.[6-8]

Compared with smoking cessation research in adults, adolescent smoking cessation research is still in its infancy. However, results from most studies published to date have been discouraging. A comprehensive review of adolescent smoking cessation trials showed a mean quit rate at 3-month follow-up of 12% compared with 7% among control groups; however, because of methodo-

logic differences among studies, comparability of outcomes was limited.[9]

Pharmacotherapy for nicotine withdrawal has greatly advanced treatment of tobacco dependence in adults. Despite growing evidence that nicotine withdrawal symptoms are an important barrier to adolescent smoking cessation,[10-12] studies of pharmacotherapy for smoking cessation in adolescents are rare.[9] Most recently, a randomized controlled trial of nicotine patch and gum demonstrated that the nicotine patch was significantly more effective than placebo at 2 weeks after the initiation of treatment, with prolonged prevalence quit rates of 17.7% and 2.5%, respectively ($P = .043$).[13] These treatment effects were not sustained at 3-month follow-up. Other nicotine patch trials for adolescent smoking cessation have failed to show significant differences among treatment groups.[14-17]

Bupropion hydrochloride, the first nonnicotine medication approved for smoking cessation, was an important advance in adult treatment of tobacco dependence and has been studied in 2 recent cessation trials for adolescents. An open-label feasibility study of sustained-release (SR) bupropion hydrochloride in adolescents with comorbid attention-deficit/hyperactivity disorder (ADHD) and nicotine dependence showed significant decreases in cigarettes smoked ($P < .001$) and carbon monoxide levels ($P = .04$) during the course of 6 weeks of treatment (150 mg twice daily), and abstinence rates of 31.25% after 4 weeks of treatment.[18] Findings are limited by a small sample size and lack of placebo control, but they support further investigation in a larger controlled trial. The second study, a randomized trial, compared combined nicotine patch and SR bupropion hydrochloride treatment (150 mg/d) with nicotine patch and placebo.[19] Abstinence rates between treatment groups were not significantly different at weeks 6 and 26 (23% and 8%, respectively, for patch and active SR bupropion; 28% and 7%, respectively, for patch and placebo); however, a decrease in smoking across groups was observed.

Bupropion has been more widely used in the treatment of attention deficit disorders in children. Notably, youths at greatest risk for developing nicotine dependence also demonstrate ADHD-like characteristics (including sensation-seeking, rebelliousness, and impulsive behaviors).[20] Early studies of bupropion in youths were for treatment of ADHD. Two studies[21,22] found bupropion comparable to methylphenidate as an effective treatment for ADHD and safe to use in children as young as 6 years. Side effects were minimal and included mild rash, drowsiness, fatigue, and nausea. None of the youths experienced seizures. Thus, given bupropion's demonstrated safety in youths and efficacy for smoking cessation in adults, we undertook a randomized, placebo-controlled study of bupropion for smoking cessation in adolescents.

The objectives of this trial were to evaluate the efficacy and safety of 2 dosages of SR bupropion hydrochloride (150 mg/d and 300 mg/d), when compared with placebo, as an aid to smoking cessation in adolescents. We hypothesized (1) that abstinence rates would be lowest in the placebo group and highest in the 300 mg group and (2) that adverse events would be negligible in all of the treatment groups but lowest in the placebo group and highest in the 300 mg group.

METHODS

STUDY DESIGN

This study was a prospective, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging phase III clinical trial with a 6-week treatment phase and blinded poststudy follow-up to week 26. The study was approved by the University of Arizona Human Subjects Committee, a certificate of confidentiality was obtained from the National Cancer Institute, and the US Food and Drug Administration granted an investigational new drug number. Written active parental informed consent and youth assent were obtained from all subjects before any study procedures.

STUDY POPULATION

Healthy, smoking adolescents were recruited from the 2 metropolitan areas of Tucson and Phoenix, Arizona, through radio and television advertisements, local tobacco control programs, shopping malls, high schools, flyers posted at teen music clubs and city bus stops, schools, and physician offices. Subjects were screened for inclusion and exclusion criteria by telephone screen, medical history, physical examination, exhaled carbon monoxide (CO) level, and urine pregnancy test (in girls). Subjects were eligible if they were 14 to 17 years of age, smoked at least 6 cigarettes per day, had an exhaled CO level greater than or equal to 10 ppm, had at least 2 previous quit attempts, weighed at least 40.5 kg, were English literate (6th-grade level), and were motivated to quit smoking. Exclusion criteria were current use of tobacco products other than cigarettes or other smoking cessation treatments; history or current diagnosis or treatment of panic disorder, psychosis, bipolar disorder, or eating disorder; substance abuse or dependence (other than nicotine) in the 3 months preceding the study; current clinical depression or ADHD; any psychoactive drug treatment within 4 weeks of the study treatment phase; increased seizure risk (personal or family history of seizure disorder, receiving treatment that increased seizure risk); and significant cardiovascular disease. Girls were excluded for pregnancy (urine pregnancy test), lactation, or unwillingness to use medically acceptable contraception. Only 1 member of a household was allowed to participate in the study concurrently.

INTERVENTION

Active study medication and identical-appearing placebo were prepackaged into 3 sets of identical-appearing blister cards in accordance with a computer-generated randomization list. At the baseline/prequit visit, a research assistant assigned the subject the next treatment number (and associated blister cards) in sequence. Study subjects and researchers remained blind to treatment group assignment throughout the study. To evaluate the success of blinding, subjects were asked to guess their treatment group at the end of treatment (week 6).

Subjects came to the research clinic for a baseline/prequit visit and were randomized to receive SR bupropion hydrochloride (150 mg/d or 300 mg/d) or placebo. Study medication was administered as 1 tablet orally once a day for the first 3 days of treatment, followed by 1 study medication tablet taken twice daily (morning and evening) for the duration of the treatment phase. Subjects attended study visits at the prequit point (when they received counseling to prepare for quitting), on the quit date, and then weekly for 7 weeks (6 weeks of treatment and 1 week after treatment cessation) to assess smoking status, adherence to the medication regimen, and safety. Study visits were conducted at a research clinic or a satellite research clinic site. Follow-up visits occurred at 12 weeks (telephone visit) and 26

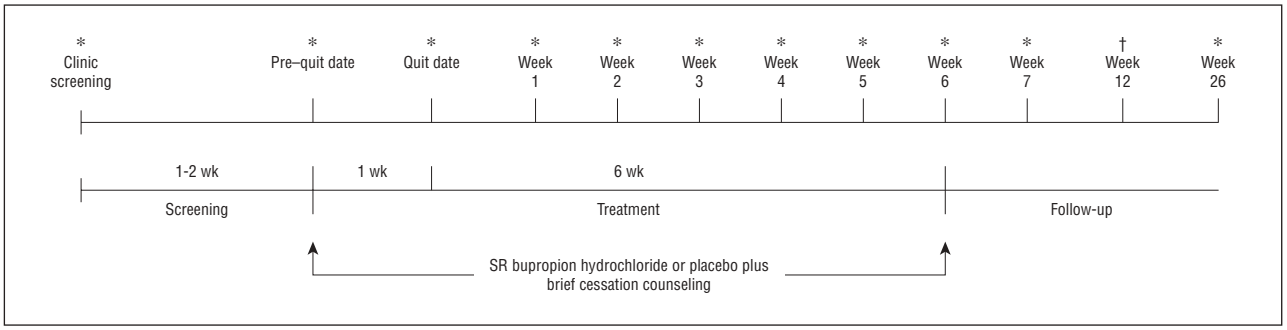

Figure 1. Study visit flow diagram. *Clinic visit. †Telephone call.

weeks after the target quit date and assessed smoking status, use of cessation aids, and adverse events. **Figure 1** shows the study visit flow.

At each visit, subjects received brief individual cessation counseling (10 to 20 minutes) standardized to address a series of topics addressing teaching skills related to changing smoking behaviors, eg, identifying social support, identifying motivations and barriers to quitting, recognition of triggers for smoking, management of nicotine craving and withdrawal symptoms, and stress management. The telephone number for the state quit line was provided for additional behavioral support if desired. Subjects who discontinued medication prematurely were encouraged to remain in the study to complete behavioral support and assessments. After the treatment phase, subjects received no further behavioral support. However, subjects could have received behavioral support from other sources. Use of additional cessation aids was queried and recorded at each visit.

SCREENING

Screening included a medical history, physical examination, measurement of vital signs, height, weight, self-identification of race/ethnicity (using classification options provided at intake), tobacco use history, and exhaled CO. A urine pregnancy test was performed on all girls.

BASELINE AND POSTRANDOMIZATION ASSESSMENTS

Smoking history at baseline included age at first cigarette, number of previous quit attempts, and smoking in the past 90 days. Nicotine dependence was assessed with a 7-item modified version of the Fagerström Tolerance Questionnaire validated for use with adolescent smokers.[23]

At each visit, subjects were queried about smoking, nicotine withdrawal, and use of any other cessation aids. Severity of 8 nicotine withdrawal symptoms (cigarette craving; depressed mood; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; increased appetite or weight gain; and sleep disturbances) was assessed with a 5-point Likert scale in which 0 indicated not at all; 1, slight; 2, moderate; 3, quite a bit; and 4, extreme. Quantitative information on tobacco, alcohol, and other drug use was collected by means of a timeline follow-back method[24,25] at each visit. Depression symptoms were assessed with the Children's Depression Inventory[26] at baseline and 2 and 6 weeks.

OUTCOME MEASURES

The primary outcome measure was abstinence at 6 weeks as measured by 7-day point prevalence abstinence and 30-day prolonged abstinence. Seven-day point prevalence abstinence was defined as self-report of not smoking any part of a cigarette or tobacco product during the week before the visit. Thirty-day prolonged abstinence was defined as self-report of not smoking any part of a cigarette or other tobacco product in the 30 days preceding the visit. Self-reported abstinence was confirmed by exhaled CO level less than 10 ppm at each visit and urinary cotinine level less than or equal to 50 µg/L (to convert cotinine to nanomoles per liter, multiply by 5.675) (enzyme multiplied immunoassay technique) at the week 2 and 6 visits.

SAMPLE SIZE

Sample size was based on the ability to detect a 15% to 20% difference between treatment groups and placebo at 6 weeks of treatment, given a projected abstinence rate of 50% in the SR bupropion hydrochloride 300 mg/d group and 15% in the placebo group. Approximately 105 subjects were needed for each treatment group to have power of 0.90 and a 1-tailed significance level of .05.

STATISTICAL METHODS

Weekly point prevalence rates were calculated for each visit by means of subjects' self-reported diaries. Subjects were considered to be actively smoking during any week in which they recorded smoking 1 or more cigarettes. Efficacy comparisons are reported for all randomized subjects on an intention-to-treat basis. Abstinence rates were compared between placebo and treatment groups by χ^2 statistics, specified a priori at a 1-tailed $\alpha = .05$ significance level. Adverse event frequencies were compared between treatment and placebo by Fisher exact test (2-tailed). Treatment groups were compared, with adjustment for other potential confounders such as sex, ethnicity, and level of addiction, by logistic regression models.

RESULTS

Between April 2, 1999, and December 31, 2002, 312 adolescents were randomized (103 in the placebo group, 105 in the 150 mg/d group, and 104 in the 300 mg/d group). The last subject follow-up was completed in June 2003. Subject flow through the study is summarized in **Figure 2**. The most common reason for study exclusion (44%) was lack of motivation to quit smoking. Characteristics of the study sample are shown in **Table 1**. Subject race/ethnicity was self-described. Of note, approximately one-half of subjects had Fagerström nicotine dependence scores of 5 or higher. A score of 6 or higher generally indicates higher levels of dependence in adults. Scores associated with higher dependence levels in adolescents have not been well studied.

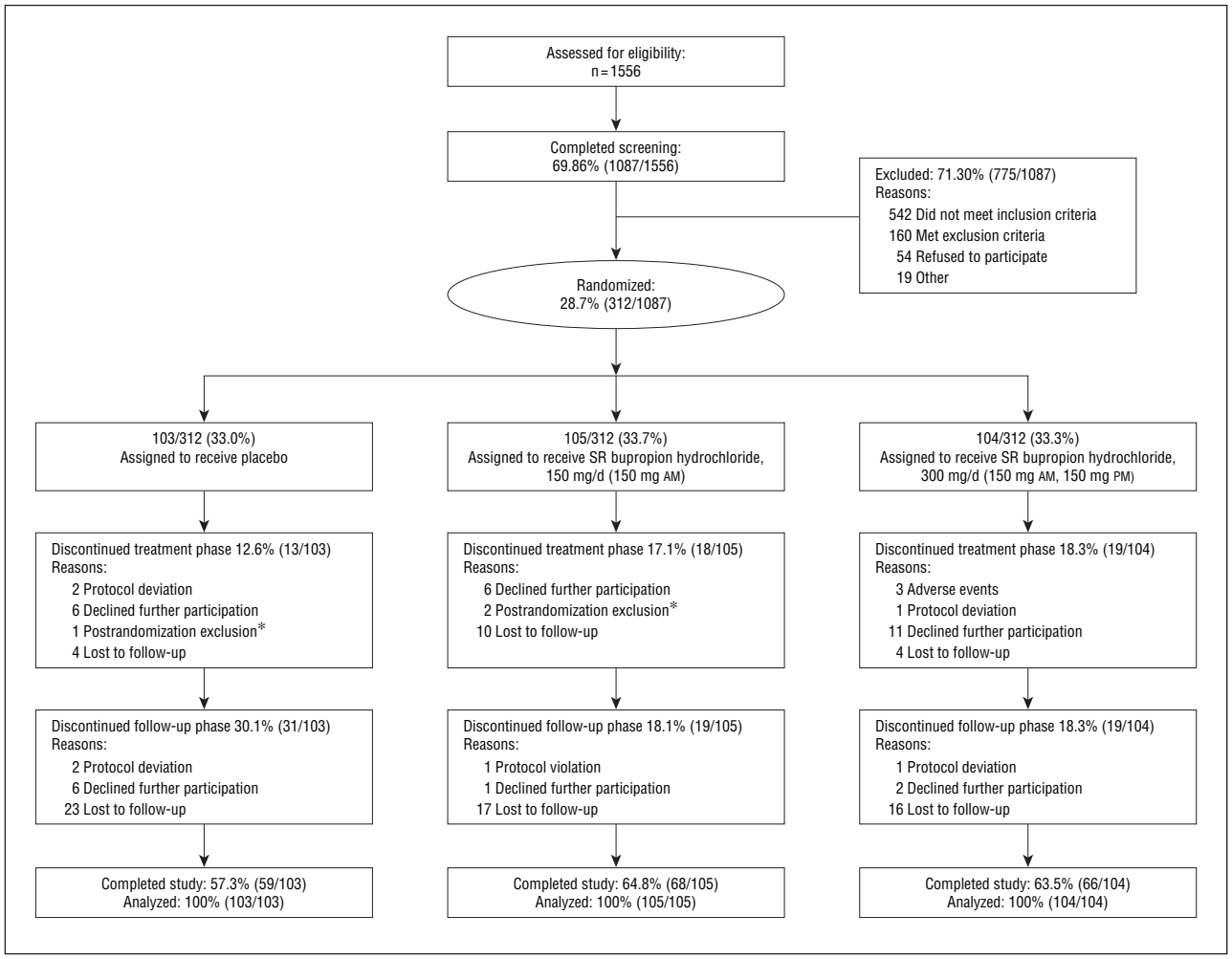

Figure 2. Subject flow diagram. SR indicates sustained release. *Subject developed an exclusionary medical condition after randomization.

Table 2 summarizes the self-reported weekly 7-day point prevalence abstinence rates. **Table 3** presents the weekly 7-day point prevalence abstinence rates verified by breath CO and urine cotinine levels (week 6 only). Sustained-release bupropion hydrochloride, 150 mg/d, did not result in quit rates significantly higher than those with placebo at any time. Average CO-confirmed quit rates over the 6 weeks of medication treatment after the quit date were 11.5% in the placebo group, 15.3% in the 150 mg/d group, and 22.6% in the 300 mg/d group. Sustained-release bupropion hydrochloride, 300 mg/d, resulted in significantly higher quit rates than placebo at all time points during medication treatment, except at weeks 2 and 4.

Six-week cotinine-verified abstinence demonstrated that only SR bupropion hydrochloride, 300 mg/d, resulted in higher quit rates than did placebo. After medication was discontinued following week 6 (end of treatment), observed differences in quit rates disappeared. There were no significant differences in either self-reported or confirmed 30-day prevalence abstinence rates. Logistic regression analyses assessing sex, ethnicity, and Fagerström score found no interactions with treatment group.

Safety was assessed on the basis of all self-reported adverse events throughout the study. Adverse events reported by at least 4% of the subjects are shown in **Table 4**. Only headache and cough occurred significantly more often in the active treatment groups than in the placebo group. Eight subjects discontinued bupropion treatment early because of the following adverse events: feeling depressed, irritable, or angry; sleep disturbance; headache; urticaria; anxiety; heart palpitations; suicide attempt; anticholinergic crisis related to recreational drug use; and pregnancy.

Two serious adverse events and 1 medically important event (defined by US Food and Drug Administration criteria for serious adverse event and medically important event) occurred during the study. A 16-year-old boy in the 150 mg/d group was hospitalized for anticholinergic crisis after deliberately ingesting Jimson weed (*Datura innoxia*) for recreational purposes. A 16-year-old girl in the 150 mg/d group was hospitalized for intentional overdose of study medication, other drugs, and alcohol in an apparent suicide attempt. Additional medical history obtained after the adverse event showed a previously undisclosed extensive history of depression and a probable eating disorder. This information, if disclosed at study screening, would have excluded the subject. The medically important event occurred in a 16-year-old girl in the placebo group who reported becoming pregnant shortly after her week 1 visit.

Table 1. Sample Demographics and Characteristics

Characteristic	No. (%)		
		Bupropion Hydrochloride	
	Placebo (n = 103)	150 mg/d (n = 105)	300 mg/d (n = 104)
Sex			
Female	43 (41.7)	56 (53.3)	44 (42.3)
Male	60 (58.3)	49 (46.7)	60 (57.7)
Age, median, y			
14	12 (11.7)	7 (6.7)	5 (4.8)
15	31 (30.1)	25 (23.8)	25 (24.0)
16	35 (34.0)	33 (31.4)	39 (37.5)
17	24 (23.3)[a]	40 (38.1)[a]	35 (33.7)
Missing data	1 (1.0)	0	0
Median age, y	16	16	16
Race/ethnicity			
African American	3 (2.9)	1 (1.0)	4 (3.8)
American Indian	3 (2.9)	5 (4.8)	2 (1.9)
Asian/Pacific Islander	2 (1.9)	2 (1.9)	0
Hispanic	16 (15.5)	17 (16.2)	13 (12.5)
White	73 (70.9)	77 (73.3)	81 (77.9)
Missing data	6 (5.8)	3 (2.9)	4 (3.8)
Education, grade			
8	3 (2.9)	4 (3.8)	2 (1.9)
9	21 (20.4)	18 (17.1)	16 (15.4)
10	26 (25.2)	26 (24.8)	27 (26.0)
11	25 (24.3)	23 (21.9)[a]	37 (35.6)[a]
12	20 (19.4)	24 (22.9)	14 (13.5)
13	1 (1.0)	0	0
Not in school	6 (5.8)	6 (5.7)	6 (5.8)
Missing data	1 (1.0)	1 (1.0)	0
Cigarettes/d, median (IQR)[b]	11 (11)	10 (8)	12 (9)
Years of smoking, median	4.0	4.0	4.0
Longest previous abstinence from smoking			
< 24 h	1 (1.0)	0	1 (1.0)
1 to 6 d	35 (34.0)	39 (37.1)	34 (32.7)
1 to 4 wk	24 (23.3)	14 (13.3)	18 (17.3)
5 wk to 6 mo	38 (36.9)	45 (42.9)	42 (40.4)
> 6 mo	1 (1.0)[c]	1 (1.0)[c]	9 (8.7)[c]
Missing data	4 (3.9)	6 (5.7)	0
Other smokers in household[d]	71 (68.9)	75 (71.4)	74 (71.2)
Fagerström score			
≤ 4	57 (55.3)	45 (42.9)	50 (48.1)
5 to 6	34 (33.0)	48 (45.7)	42 (40.4)
≥ 7	12 (11.7)	12 (11.4)	11 (10.6)
Missing data	0	0	1 (1.0)

Abbreviations: CI, confidence interval; IQR, interquartile range.
[a] Differences between groups, $P < .05$.
[b] Excluding 8 cases where the unit is "per month" rather than "per day."
[c] Differences between groups, $P < .01$.
[d] Data represent those reporting at least 1 other smoker in the household.

COMMENT

The present study has a number of strengths: dose-response study design, biochemical verification of abstinence, large sample size, and community-recruited subjects. The dose-response design was particularly important because key pivotal research on the efficacy of SR bupropion hydrochloride for adult cessation raised questions about a sufficient effect from 150 mg/d rather than 300 mg/d dosing.[27-29] We hypothesized that youths, on average, would weigh less than adults. Therefore, assessing equivalency of a lower dose—on the basis of either efficacy or tolerability—is essential. Our results indicate that only the 300 mg/d dosage was more efficacious for smoking cessation than placebo, and the effect appeared to be limited to the treatment phase. At baseline, the 300 mg/d group had significantly more adolescents who were older, had a history of longer previous quit attempts, and smoked more cigarettes. We interpreted these differences as being indicative of adolescents who are older, more established smokers, who are now trying to quit. We believe these differences would tend to bias against finding a treatment effect; thus, we are more confident in the significantly higher quit rates for the 300 mg/d group.

Biochemical verification of abstinence during the medication treatment phase of the study and at the 26-week follow-up visit resulted in quit rates that were consistent with, but an average of 14% to 23% lower than, self-reported outcomes. We are thus more confident in our outcomes as a result of verification.

The sample size was comparatively large for a youth smoking cessation medication study, thus resulting in greater power to detect meaningful differences, although we observed some possible trends (eg, the comparison between placebo and 150 mg) that will require even larger studies. However, a critical issue in conducting a larger study is the difficulty of recruiting youths into cessation studies.[30]

Community-based recruitment from real-world teen environments (schools, shopping malls, and teen clubs) was an essential strategy developed in response to inadequate subject accrual by conventional methods of clinical trial recruitment. Community-based recruitment ultimately became a significant study strength because it resulted in a more diverse study population (including minorities and youths not in school), thus increasing the study's external validity. However, we still struggled to achieve the required sample size. The increased diversity of the sample notwithstanding, generalizability is limited in that only 28.7% of subjects who completed initial screening were randomized. The most common reason for exclusion (44%) was lack of motivation to quit smoking. Future studies will need to consider recruitment challenges when planning timelines and recruitment resources.

Study limitations include modification of the study protocol (follow-up shortened from 52 weeks after the quit date to 26 weeks) to adjust for recruitment changes and a prolonged accrual period. Some characteristics of the more diverse community-recruited subjects could be associated with lower cessation rates. However, randomization should have equally distributed subject characteristics across treatment groups. Thus, we do not believe the main study outcomes were related to differences in recruitment.

The use of exhaled CO for biochemical confirmation of abstinence for all but the week 2 and week 6 (end-of-treatment) assessments is a limitation, due to CO's short half-life. Although the subjects were daily smokers (≥6 cigarettes per day), the cotinine-confirmed abstinence rates at the end of treatment were 50% to 65% lower than the CO-confirmed rates. The implication is that, even for ado-

Table 2. Seven-Day Point Prevalence Abstinence, Self-report

Week After TQD	No./Total No. (%) of Subjects Not Smoking			*P* Value		
		Bupropion Hydrochloride				
	Placebo	150 mg/d	300 mg/d	Overall	Placebo vs 150 mg	Placebo vs 300 mg
1	6/95 (6)	7/88 (8)	14/88 (16)	.04[a]	.33	.02[a]
2	11/88 (12)	11/82 (13)	18/92 (20)	.18	.43	.10
3	10/85 (12)	16/81 (20)	23/87 (26)	.03[a]	.08	.008[a]
4	12/83 (14)	20/85 (24)	19/82 (23)	.13	.07	.08
5	14/80 (18)	16/78 (21)	30/80 (38)	.004[a]	.32	.01[a]
6	18/89 (20)	23/84 (27)	28/83 (34)	.07	.14	.02[a]
7	17/72 (24)	17/79 (22)	26/76 (34)	.08	.38	.08
12	14/55 (25)	11/61 (18)	14/57 (25)	.29	.17	.46
26	6/58 (10)	4/64 (6)	11/65 (17)	.08	.20	.15

Abbreviation: TQD, target quit date.
[a] $P < .05$.

Table 3. Seven-Day Point Prevalence Abstinence, Confirmed by Carbon Monoxide or Cotinine[a]

Week After TQD	No./Total No. (%) of Subjects Not Smoking			*P* Value		
		Bupropion Hydrochloride				
	Placebo	150 mg/d	300 mg/d	Overall	Placebo vs 150 mg	Placebo vs 300 mg
Carbon monoxide						
1	5/95 (5)	5/88 (6.)	13/88 (15)	.02[b]	.45	.02[b]
2	8/88 (9)	10/82 (12)	17/92 (18)	.08	.26	.04[b]
3	8/85 (9)	13/81 (16)	20/87 (23)	.03[b]	.10	.008[b]
4	11/83 (13)	17/85 (20)	18/82 (22)	.16	.12	.07
5	13/80 (16)	12/78 (15)	23/80 (29)	.03[b]	.44	.03[b]
6	14/89 (16)	19/84 (23)	24/83 (29)	.06	.12	.02[b]
7	13/72 (18)	14/79 (18)	19/76 (25)	.23	.48	.15
26	6/58 (10)	2/64 (3)	9/65 (14)	.049[b]	.05	.28
Cotinine						
6	5/89 (6)	9/84 (11)	12/83 (14)	.08	.11	.03[b]

Abbreviation: TQD, target quit date.
[a] Abstinence was confirmed if exhaled carbon monoxide level was less than 10 ppm or urinary cotinine level was less than or equal to 50 µg/L (to convert cotinine to nanomoles per liter, multiply by 5.675).
[b] $P < .05$.

Table 4. Treatment-Emergent Adverse Events[a]

Adverse Event	No. of Adverse Events/No. of Subjects (%)		
		Bupropion Hydrochloride	
	Placebo	150 mg/d	300 mg/d
Headache	56/103 (54.4)	52/105 (49.5)[b]	46/104 (44.2)[b]
Cough	24/103 (23.3)	17/105 (16.2)	13/104 (12.5)[b]
Throat symptom/ concern	24/103 (23.3)	18/105 (17.1)	18/104 (17.3)
Sleep disturbance	11/103 (10.7)	12/105 (11.4)	15/105 (14.3)
Nausea	10/103 (9.7)	18/103 (17.5)	10/103 (9.7)

[a] Adverse events experienced at least once by any subject during or immediately after the treatment period by more than 4% of subjects in any group are listed in decreasing order according to overall frequency.
[b] $P < .05$ vs placebo group, Fisher exact test.

lescents who report daily smoking, the cotinine rather than CO level should be used to confirm abstinence in cessation trials.

Another possible study limitation is that study subjects received compensation for study participation, potentially influencing motivation for initial study enrollment and continued participation. Although this could influence overall motivation to quit, randomization would have resulted in a relatively equal distribution across the study conditions, so that motivation would not explain the differences between treatment groups.

The ability of study subjects to guess their treatment group, thus undermining the blind, is a potential limitation. However, only 10 subjects (9.6%) in the 300 mg group accurately guessed their treatment assignment. Across all treatment groups, there were no significant differences in the proportion of subjects who accurately guessed their treatment group.

CONCLUSIONS

This study demonstrates that SR bupropion hydrochloride at 300 mg/d plus brief behavioral counseling has short-

term efficacy in helping adolescent smokers quit. However, abstinence rates at the end of treatment were less than those reported in bupropion cessation studies in adults. The 150 mg/d dosage did not result in increased quit rates but demonstrated a possible trend in the direction of increased cessation relative to placebo. Both dosages were generally well tolerated. These results are critically important because few effective treatment options are available for adolescent smokers who want to quit.

Despite the positive end-of-treatment outcome, subjects tended to relapse soon after discontinuing medication. This suggests a need to evaluate a longer dosing regimen in adolescent smokers, eg, 12 weeks, which would be consistent with current recommendations for treatment of adult smokers. In addition, further research is needed on interventions to prevent relapse, once medication treatment has ended. Nonetheless, this study provides hope for helping a generation of smokers quit before they become adults.

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