Safety and Efficacy of the Nicotine Patch and Gum for the Treatment of Adolescent Tobacco Addiction

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ABSTRACT. *Objectives.* **To determine the safety and efficacy of the nicotine patch and gum for adolescents who want to quit smoking.**

Design. **Double-blind, double-dummy, randomized, 3-arm trial with a nicotine patch (21 mg), nicotine gum (2 and 4 mg), or a placebo patch and gum; all participants received cognitive-behavioral group therapy.**

Setting. **Inner-city, outpatient clinic on the East Coast.**

Subjects. **Thirteen- to 17-year-old adolescents who smoked ≥10 cigarettes per day (CPD), scored ≥5 on the Fagerström Test of Nicotine Dependence, and were motivated to quit smoking.**

Intervention. **Twelve weeks of nicotine patch or gum therapy with cognitive-behavioral therapy, with a follow-up visit at 6 months (3 months after the end of treatment).**

Main Outcome Measures. **Safety assessed on the basis of adverse event reports for all 3 groups, prolonged abstinence, assessed through self-report and verified with exhaled carbon monoxide (CO) levels of ≤6 ppm, in intent-to-treat analyses, and smoking reduction (CPD and thiocyanate concentrations) among trial completers.**

Results. **A total of 120 participants were randomized (72% white, 70% female; age: 15.2 ± 1.33 years; smoking: 18.8 ± 8.56 CPD; Fagerström Test of Nicotine Dependence score: 7.04 ± 1.29) from 1999 to 2003. Participants started smoking at 11.2 ± 1.98 years of age and had been smoking daily for 2.66 ± 1.56 years; 75% had at least 1 current psychiatric diagnosis. Mean compliance across groups was higher for the patch (mean: 78.4–82.8%) than for the gum (mean: 38.5–50.7%). Both the patch and gum were well tolerated, and adverse events were similar to those reported in adult trials. Changes in mean saliva cotinine concentrations throughout treatment were not statistically significant. Intent-to-treat analyses of all randomized participants showed CO-confirmed prolonged abstinence rates of 18% for the active-patch group, 6.5% for the active-gum group, and 2.5% for the placebo group; the difference between the active-patch and placebo arms was statistically significant. There was no significant effect of patch versus gum or gum versus placebo on cessation outcomes. Abstinence rates at the 3-month follow-up assessment were sustained but were not significantly associated with treatment group. Mean smoking rates, but not CO or thiocyanate concentrations, decreased significantly in all 3 arms but not as a function of treatment group.**

Conclusions. **Nicotine patch therapy combined with cognitive-behavioral intervention was effective, compared with placebo, for treatment of tobacco dependence among adolescent smokers. Decreases in the numbers of cigarettes smoked appeared to be offset by compensatory smoking. Additional study of nicotine gum, with enhanced instructional support, is needed to assess its efficacy among adolescent smokers. *Pediatrics* 2005; 115:e407–e414. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1894; *treatment, adolescent, tobacco, nicotine patch, nicotine gum, cessation, smoking reduction.***

ABBREVIATIONS. CPD, cigarettes per day; NRT, nicotine replacement therapy; FTND, Fagerström Test of Nicotine Dependence; CO, carbon monoxide; IDR, incidence density ratio; CI, confidence interval; OR, odds ratio.

After having peaked in the late 1990s, smoking prevalence among adolescents declined slightly, although remaining high. Percentages of eighth-, 10th-, and 12th-graders who reported having smoked in the past 30 days were 10.2%, 16.7%, and 24.4%, respectively, in 2003.[1] More importantly, tobacco addiction develops among adolescent smokers, and they experience withdrawal symptoms similar to those of adult smokers when they try to abstain from smoking.[2] A large proportion of adolescent smokers have tried unsuccessfully to stop smoking at least once, most frequently with acute abstinence ("cold turkey") methods,[3] and many desire treatment to help with cessation.[4] Most adolescents with established smoking habits continue to smoke as adults and incur both short-term and long-term health consequences, including premature death.[5] Therefore, safe and effective smoking cessation interventions for adolescent smokers are critically needed.

Although several informative reviews of the adolescent smoking-cessation literature have been published in recent years, one challenge remains, namely, how best to tailor the setting and modalities for cessation interventions for youths.[6–8] Various counseling and behavioral, classroom-based approaches have included infrequent and low-level smokers with more intense smokers, with some yielding encouraging short-term quit rates of 30 to 50%.[9,10] Although advocated by expert opinion in a

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clinical practice guideline,[11] very few pharmacologic interventions have been evaluated for treating dependent teenage smokers. In open-label trials of the nicotine patch in combination with group counseling support, abstinence rates remained very low (4.5–11.5%).[12,13] A small-sample ($N = 16$), open-label, bupropion study reported an abstinence rate of 31% after 4 weeks of treatment.[14] Two randomized, adolescent, patch trials have been reported. In the first, participants were randomized to the patch or placebo, in combination with intense cognitive-behavioral and contingency management therapies to reinforce tobacco abstinence. Cessation rates reached 18% at 3 months, but no significant treatment effect was observed.[15] In the other trial, teen smokers were assigned randomly to either patch plus bupropion or patch plus placebo, with weekly group skills training. Abstinence rates measured at weeks 10 and 26 were 23% and 8% for the patch plus bupropion group and 28% and 7% for the patch plus placebo group, respectively.[16] Although no treatment effect was observed, these cessation rates were encouraging.

Relatively low abstinence rates in previous treatment trials with addicted adolescent smokers prompted us to evaluate biochemically verified reduced smoking as a treatment outcome variable. Treatment-generated reductions in smoking rates among adults have been reported with pharmacologic methods[17–19] and demonstrate the potential for deferred quitting.[20,21] Despite limited effects on cessation in the open-label youth trials,[12,13] transdermal nicotine therapy was associated with significant self-reported decreases in cigarette consumption. This type of effect has been linked to a reduction of adolescents' smoking in the long term,[5] which might translate into health benefits on a population basis if accompanied by decreases in toxin exposure.[22] Moreover, in a longitudinal trial with Swiss youths, a reduction of 5 cigarettes per day (CPD) during adolescence doubled the chances of being abstinent 3 years later.[23] As suggested in a previous report, lower systemic support for quit attempts, and potentially less motivation, preparation, and success in achieving total cessation among adolescents, compared with adult smokers, might prompt the consideration of tobacco exposure reduction as an intermediate treatment goal for adolescent smokers.[24] Gradual reduction of smoking might also appeal to subgroups of teen smokers who smoke to self-medicate negative cognitive or affective states.[23,25]

On the basis of the clinical practice guideline[11] and the observation that youths do purchase and have access to nicotine replacement therapy (NRT),[1,26] we designed this pilot trial to determine the safety and preliminary efficacy of the nicotine gum and patch, used in combination with cognitive-behavioral group therapy,[27] to help young smokers achieve cessation. Because of the growing interest in therapies that might aid in reducing smoke exposure and the possibility that many addicted adolescent smokers might not be ready for complete cessation,[23,24] we were also interested in determining whether treatment could produce a substantial reduction in smoking rates among trial-completers.

METHODS

Sample

This study was approved by the National Institute on Drug Abuse institutional review board and was conducted in Baltimore, Maryland. Outreach and recruitment were performed from September 1999 to September 2003, through various media (print, audiovisual, and electronic) advertisements and through various community channels, such as schools and churches. Adolescent smokers desiring to quit were encouraged to call for a structured telephone interview, to determine their initial preeligibility. Callers who reported major physical health problems or untreated acute psychiatric problems were excluded. Only participants who were able to discuss their smoking with their parent/guardian, were motivated to quit (>5 on a 10-point integer scale), and were planning to remain in the area for the duration of the trial were invited for on-site screening.

Final eligibility was determined after an on-site history recording, physical examination, and basic laboratory screening. Adolescents 13 through 17 years of age who were in general good health, had smoked ≥10 CPD for ≥6 months, had a minimal score of 5 on the Fagerström Test of Nicotine Dependence (FTND), and were motivated to stop smoking were eligible to participate. Pregnancy, lactation, chronic skin conditions, use of other tobacco products, and current use (within the past 30 days) of medications for smoking cessation (eg, NRT or bupropion) were reasons for exclusion. Drug or alcohol dependence other than nicotine and current mania, psychosis, and acute depression, according to the Diagnostic Interview of Children and Adolescents,[28] which was based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, were also exclusion criteria. However, candidates taking psychotropic medications not prescribed for smoking cessation were included in the trial.

Procedures

Adolescents who qualified through a 10- to 15-minute telephone screening were invited, with a parent or guardian, to an orientation meeting in which an overview of the study and clinic functioning was presented. Signed informed assent and consent were obtained from all adolescents and their parents or legal guardians, respectively. A "universal" Fagerström questionnaire, which included the FTND and more youth-appropriate versions of the questionnaire, and other baseline sociodemographic assessments were completed. Expired-air carbon monoxide (CO) testing (Vitalograph, Lenexa, KS) was performed, blood was drawn, and saliva was collected for measurement of baseline (while the subjects were smoking their usual numbers of cigarettes) nicotine, cotinine, and thiocyanate concentrations. Female adolescents of childbearing potential were required to have a negative pregnancy test before being randomized. The target quit date was set 1 week after the 2 baseline clinic visits.

On the quit date, participants were instructed in the use of the 21-mg nicotine patch and gum (2 mg if smoking ≤24 CPD or 4 mg if smoking >24 CPD), according to Food and Drug Administration labeling, and were given self-help materials from the package insert used for the over-the-counter products. Participants weighing <100 pounds (45 kg) and smoking <20 CPD at baseline received the 14-mg patch. GlaxoSmithKline (Research Triangle Park, NC) provided study medication (Nicoderm, 21 mg and 14 mg; Nicorette, 2 mg and 4 mg) but did not participate in the study design, study performance, or data analysis. Participants were told to use the gum as needed, with the approximate goal of using one half their baseline reported CPD values in numbers of pieces of gum (eg, 10 pieces of gum for smokers smoking 1 pack per day, as a guideline) for the beginning of treatment. For this double-blind study, adolescents were randomized to 1 of 3 groups according to an algorithm held by the National Institute on Drug Abuse Pharmacy, with true replacement of trial-noncompleters. Because both the patch and gum are used commonly, the 3 groups included (1) active patch and placebo gum, (2) active gum and placebo patch, and (3) placebo gum and placebo patch. Adolescents were asked to complete a weekly questionnaire recording the number of cigarettes smoked, tobacco craving, and symptoms of tobacco withdrawal and depression.[29] Nurses recorded vital

signs, including height and weight, and provided minimal individual counseling (3-4 minutes) to address possible medication side effects and proper use of the nicotine patch and gum. Trained study assistants aided in data collection. After the 2 baseline visits, participants attended 11 visits over a total of 12 weeks of treatment (Fig 1 illustrates the study timeline). At each visit, vital signs and exhaled CO were measured and saliva specimens were collected for later cotinine and thiocyanate assays. Assays were completed by Labstat, Inc (Kitchener, Ontario, Canada). Used and unused patches were collected, and a new supply was dispensed. Participants were queried regarding any adverse reactions and concomitant medication use since the last visit. Information on adverse events was elicited through open-ended questions (eg, "How have you been feeling since the last visit") and also through direct prompting of teens to indicate whether specific side effects on a questionnaire had been experienced. A monthly urine pregnancy test was performed for female participants. Subjects returned at 6 months (3-month posttreatment follow-up visit) for assessment of self-reported smoking status and expired-air CO measurements; saliva samples were collected for quantification of cotinine and thiocyanate. Participants attended a 45-minute cognitive-behavioral group therapy session led by a trained social worker at the end of each treatment visit. The aim of the cognitive-behavioral therapy was to help participants identify and address specific factors that led either to smoking or to maintaining abstinence from smoking behavior and manage life stressors better by using effective, adaptive, coping skills.[27] Study participants were compensated with $90 for the baseline assessment and $135 after study completion for research activities other than treatment.

Data Analyses

Given 3 study groups, for a power of .80 and an α level of .05, based on reported values for adult populations[30] and assuming a 70% reduction of smoke exposure in the active-medication groups, the approximate sample size needed to perform an analysis of variance for the main outcome variable (saliva thiocyanate concentrations) was estimated at 17 for each group. Given an anticipated attrition rate of 55%, 40 patients for each group were required to obtain a total of 51 completers. The sample of 53 completers slightly exceeded the 51 planned.

The other study end points were measures of cessation, ie, point prevalence abstinence and prolonged abstinence. For weekly point prevalence abstinence rates, subjects were considered abstinent from smoking if they self-reported not smoking during the 7 days before a visit and had an expired-air CO level of $\leq$6 ppm at that visit. Subjects missing visits for any reason were considered to be smoking at the time of the missed visits. Prolonged abstinence was defined as point prevalent abstinence maintained throughout the trial, after an initial 2-week grace period after the quit date.[31,32]

Self-reported smoking rates reported at each visit were summarized as mean CPD values and calculated as change from baseline. The data were summarized with weekly means for each of the 6 weeks of the medication phase and at the 12-week and 6-month follow-up visits.

The 3 treatment groups were compared with respect to demographic and smoking history variables with analysis of variance for continuous variables and χ^2 tests for categorical variables. Any variable found to be associated with treatment group assignment was considered a potential confounder and was included as a covariate in outcome analyses if also associated with the outcome measure. Nonparametric survival analysis techniques (log-rank and Wilcoxon tests) were used to determine whether treatment groups differed with respect to retention. Incidence density ratios (IDRs) were calculated to compare rates of adverse events in each active-treatment group with those in the placebo group; the IDR equals the adverse event count per person-weeks of follow-up monitoring for each active-medication group divided by the adverse event count per person-weeks of follow-up monitoring for the placebo group. When the rate of adverse events in either active-medication arm exceeded that in the placebo arm (ie, IDR $>$ 1), a 1-sided hypothesis test was used to determine whether the excess was statistically significant ($P < .05$). The normal approximation to the binomial was used when warranted; otherwise, an exact binomial test was performed.

Fisher's exact tests, χ^2 tests, and logistic regression analyses were used to assess the effect of treatment group assignment on smoking cessation (both prolonged abstinence and point prevalence abstinence). Treatment groups were coded such that each active-medication arm was compared with placebo. Fisher's exact tests and χ^2 tests were performed to determine whether frequencies of participants achieving abstinence were associated with treatment group assignment, with contingency tables, and whether maximal likelihood parameter estimates from logistic regression models differed from 0; the treatment effect was considered statistically significant if the P value was $<.05$. Analysis of variance with planned contrasts (patch versus placebo and gum versus placebo) was used to determine whether continuous outcome measures (compliance rates, reductions in CPD values, CO levels, and saliva thiocyanate levels, and withdrawal symptoms) were associated with treatment group assignment. Compliance for the patch was defined as the number of patches used for the first 30 days of treatment divided by 30; compliance for the gum was defined as the number of reported pieces of gum used during the first 30 days divided by one half the baseline reported CPD value times 30. Paired t tests were used to determine the significance of changes observed in continuous measures of smoking during the trial (before/after differences in CPD values, CO levels, and saliva thiocyanate levels). For cessation end points, an intent-to-treat analysis was performed that included all participants randomized ($n = 120$); participants who dropped out were assumed to have been smoking. For all other end points, the analysis included participants for whom data were available.

RESULTS

Participant Characteristics

Of 1347 adolescents who telephoned the clinic in response to advertisements, 329 were preeligible in telephone screenings and 159 presented for on-site screening, as described in a separate report.[33] Of the 159 adolescents who presented for enrollment, 39 (24.5%) were not randomized, after on-site evaluations indicated their ineligibility (Fig 2).

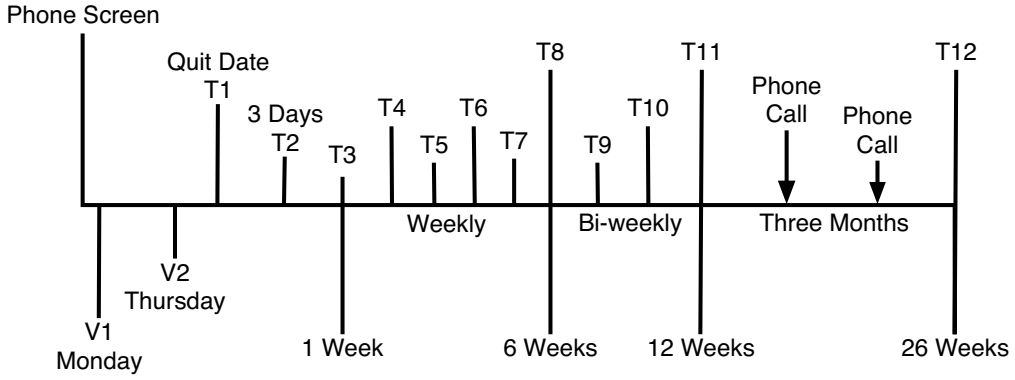

Fig 1. Study timeline.

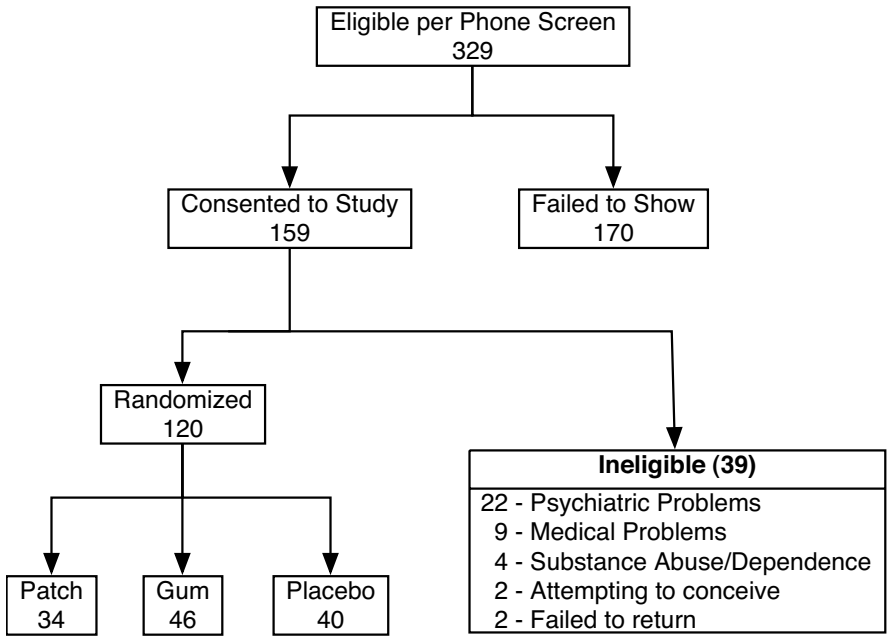

Fig 2. Participant enrollment flow chart.

One hundred twenty participants were randomized to receive treatment; 53 completed the study. Overall, randomized subjects were 15.2 ± 1.33 years of age, 72.5% white, and 70.0% female. At the time of admission, they smoked an average of 18.8 ± 8.56 CPD and had a mean FTND score of 7.04 ± 1.29, indicating high dependence. Participants started smoking at 11.2 ± 1.98 years of age and had been smoking daily for 2.66 ± 1.56 years. Table 1 provides the characteristics according to treatment group. Only the age at which subjects started smoking was significantly associated with treatment group assignment [$F(2111) = 4.25$, $P = .017$]; participants assigned to receive the patch started smoking at a later age. The age at which subjects started smoking was significantly associated with prolonged abstinence and CPD reduction; therefore, this variable was used as a covariate in analyses of these outcomes.

Baseline psychiatric assessments revealed that 90 subjects (75%) had at least 1 current psychiatric diagnosis, according to the Diagnostic Interview for Children and Adolescents.[28] The most frequently represented categories were oppositional defiant disorder (40%), conduct disorder (15%), attention-deficit/hyperactivity disorder (current: 7%; previous: 11%), and premenstrual dysphoric disorder (11%). The percentages of participants with at least 1 psychiatric diagnosis in each treatment group were as follows: patch, 64%; gum, 75%; placebo, 85%. Several applicants were enrolled in the trial while taking prescribed psychotropic medications, including (categories not mutually exclusive) sertraline (6 subjects), methylphenidate (4 subjects), paroxetine (4 subjects), fluoxetine (3 subjects), hydroxyzine (2 subjects), citalopram (2 subjects), trazodone (2 subjects), venlafaxine (2 subjects), risperidone (1 subject), and olanzapine (1 subject).

The proportions of randomized participants who completed the study were 41.3% (19 of 46 subjects) for the gum group, 52.9% (18 of 34 subjects) for the patch group, and 40.0% (16 of 40 subjects) for the placebo group; differences in study completion rates were not statistically significant (χ^2 test). Treatment group differences in retention times were not statistically significant ($P = .71$ with log-rank test and $P = .60$ with Wilcoxon test for homogeneity of survival curves).

Safety

Safety was assessed on the basis of all self-reported adverse events throughout the trial and nicotine and cotinine concentrations in saliva. Of 745 total adverse events documented during the trial, the frequencies of events, in descending order, were as follows: pruritus, 130 cases; erythema, 111 cases; headache, 86 cases; fatigue, 67 cases; viral infection, 63 cases; insomnia, 43 cases; cough, 32 cases; nausea, 31 cases; jaw pain, 30 cases; anxiety, 26 cases; sore throat, 24

TABLE 1. Participant Characteristics ($N = 120$)

	Patch ($n = 34$)	Gum ($n = 46$)	Placebo ($n = 40$)
Age, y	15.4 ± 1.41	15.0 ± 1.31	15.2 ± 1.29
Female, %	61.8	69.6	77.5
White, %	79.4	65.2	75.0
FTND score	7.00 ± 1.11	7.09 ± 1.39	7.00 ± 1.32
CPD	17.7 ± 6.45	18.9 ± 8.96	19.6 ± 9.70
Age started smoking, y*	12.1 ± 1.87	11.0 ± 1.99	10.9 ± 1.91
Years smoked daily	2.57 ± 1.29	2.73 ± 1.88	2.66 ± 1.35

* $P < .05$.

cases; hiccup, 22 cases; dyspepsia, 22 cases; shoulder or arm pain, 18 cases; dizziness, 15 cases; congestion, 10 cases; edema, 10 cases; constipation, 3 cases; diarrhea, 2 cases; other, 18 cases. Active medication was associated with a statistically significant increase in adverse events for the following symptom categories: sore throat (gum versus placebo, IDR = 4.79, $P = .0007$), hiccups (gum versus placebo, IDR = 2.79, $P = .014$), shoulder/arm pain (patch versus placebo, IDR = 4.63, $P = .0011$), pruritus (patch versus placebo, IDR = 1.63, $P = .033$; gum versus placebo, IDR = 1.95, $P = .003$), and erythema (patch versus placebo, IDR = 1.97, $P = .0045$). Table 2 provides the frequency of adverse events according to treatment arm. Overall, the highest (mean ± SD) saliva cotinine concentrations were observed at the 2.5-month postquit visit (T10), but the increase over baseline was not significant in either treatment group (data not shown).

Cessation

The proportions of participants who achieved prolonged abstinence (continuous abstinence as of 2 weeks after randomization) were as follows: patch group, 6 of 34 subjects (17.7%); gum group, 3 of 46 subjects (6.5%); placebo group, 1 of 40 subjects (2.5%) (Fig 3). For prolonged abstinence, a trend toward statistical significance was found for the overall effect of treatment (2-tailed Fisher's exact test, $P = .066$). Two-tailed Fisher's exact tests showed that the direct comparison between patch and placebo was statistically significant ($P = .043$), whereas the comparison between gum and placebo was not statistically significant ($P = .62$). Post hoc comparisons of the patch and gum groups revealed no statistically significant difference. The odds ratio (OR) of prolonged abstinence for the patch group, compared with the placebo group, was 8.36 (95% confidence interval [CI]: 0.95–73.3; $P = .055$) and that for the gum group, compared with the placebo group, was 2.72 (95% CI: 0.27–27.3; $P = .39$); adding the age at which the subjects started smoking as a covariate in the logistic regression model did not alter the results substantively.

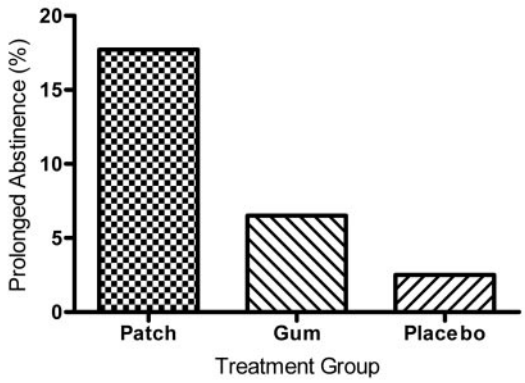

Fig 3. Prolonged abstinence at 3 months, according to intent-to-treat analysis.

In addition to prolonged abstinence, we examined point prevalence abstinence at 3 time points, ie, 1 week after the quit date, at the end of the study, and 3 months after study completion. At 1 week after the quit date, a time at which patient follow-up monitoring might begin in a standard medical practice, proportions of abstinent participants were as follows: patch group, 9 of 34 subjects (26.5%); gum group, 8 of 46 subjects (17.4%); placebo group, 2 of 40 subjects (5.0%). The OR of point prevalence abstinence for the patch group, compared with the placebo group, was 6.84 (95% CI: 1.36–34.33; $P = .02$) and that for the gum group, compared with the placebo group, was 4.00 (95% CI: 0.80–20.1; $P = .09$). Two-tailed Fisher's exact tests found the effect for patch versus placebo to be statistically significant ($P = .030$), whereas the effect for gum versus placebo was not ($P = .45$). Post hoc comparison of the patch and gum groups revealed no statistically significant difference in rates of point prevalence abstinence at 1 week after the quit date. The proportions of abstinent participants according to group did not change from study completion to 3 months after study comple-

TABLE 2. Adverse Events Among Randomized Participants ($N = 120$), Listed In Order of Decreasing Overall Frequency, According to Treatment Group

	Patch (476 person-wk)	Gum (552.1 person-wk)	Placebo (439.9 person-wk)	Elevated in Active-Medication Group, Compared with Placebo
Pruritus	44	61	25	Patch, $P = .033$; gum, $P = .003$
Erythema	49	39	23	Patch, $P = .0045$
Headache	24	26	36	
Fatigue	15	20	32	
Viral infection	14	30	19	
Insomnia	13	17	13	
Cough	9	15	8	
Nausea	10	10	11	
Jaw pain	10	12	8	
Anxiety	6	13	7	
Sore throat	3	18	3	Gum, $P = .0007$
Hiccups	4	14	4	Gum, $P = .014$
Dyspepsia	4	10	8	
Shoulder or arm pain	15	0	3	Patch, $P = .00011$
Dizziness	3	3	9	
Congestion	3	3	4	
Edema	4	2	4	
Constipation	3	0	0	
Diarrhea	0	0	2	

tion: patch, 20.6%; gum, 8.7%; placebo, 5%. Point prevalence abstinence results were highly concordant at the end of treatment (T11) and at the 3-month follow-up evaluation (T12). In the patch group, 1 participant was abstinent at T11 but not at T12 and another participant was abstinent at T12 but not at T11; the same was true for the gum group. For the placebo group, 2 participants were abstinent at T11 but not T12 and another 2 were abstinent at T12 but not T11. At study completion (T11) and 3 months after study completion (T12), logistic regression analyses showed a trend toward significance for the effect of the patch, compared with placebo (OR: 4.93; 95% CI: 0.95–25.6; $P = .058$), and no significance for the effect of gum (OR: 1.81; 95% CI: 0.31–10.4; $P = .51$). Figure 4 displays point prevalence abstinence, according to intent-to-treat analysis, at each visit throughout the study.

Reduction

Percent reduction was calculated with the following formula: % reduction = 100 × [(follow-up value − baseline value)/baseline value]. Therefore, a negative sign indicates reduction and a positive sign denotes increase. Mean reductions in self-reported CPD values exceeding 80% were observed for all 3 treatment groups at the end of the treatment phase; these reductions were significantly different from 0 with paired *t* tests. However, analysis of variance with contrasts showed that these decreases were not associated with treatment group assignment (Table 3). Adding the age at which subjects started smoking as a covariate did not alter the findings. The mean changes in both expired CO and saliva thiocyanate levels did not differ from 0 and did not differ according to treatment group (Table 3).

Compliance

Mean compliance rates based on daily use of the patch were 78.4% for the patch group, 82.8% for the gum group, and 80.9% for the placebo group. Analyses of variance showed no significant differences among treatment groups in the proportions of patches used.

Compliance rates for gum use during the first month of the trial (based on the recommended amount of use according to pretreatment CPD values) were 42.1% for the patch group, 38.5% for the gum group, and 50.7% for the placebo group. Analysis of variance with planned contrasts showed that compliance in the gum group differed significantly from that in the placebo group [$F(1100) = 5.59$, $P = .020$].

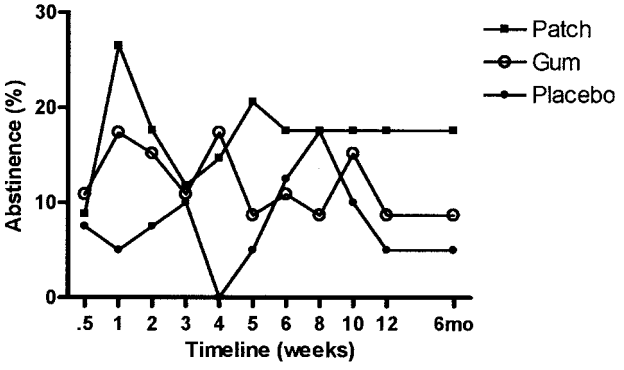

Fig 4. Point prevalence abstinence, according to intent-to-treat analysis.

DISCUSSION

The main finding from our study was that the nicotine patch was significantly more effective than placebo in helping dependent adolescent smokers receiving cognitive-behavioral therapy quit smoking (prolonged abstinence). Despite the absence of significant group differences in rates measured at the end of treatment, there was a trend toward higher point prevalence abstinence rates in the patch group, compared with the placebo group, that was sustained at the 3-month follow-up visit. The large effect size (OR: 8.36) for the comparison of the patch versus placebo for prolonged abstinence suggests a clinically significant effect; however, the wide CI (95% CI: 0.95–73.3) indicates a lack of statistical power. This is not surprising, because the study was designed to have sufficient statistical power to detect a significant reduction but not a cessation effect. Future studies of NRT among adolescent smokers should be designed to detect group differences in abstinence rates.

Despite substantial psychiatric comorbidity in our recruited sample, cessation rates obtained in this study were comparable to those reported previously from youth studies[12,15,34] and slightly lower than those from adult studies (15–28% at 6 months) with NRT.[35–37] Unlike cessation, reductions in cigarette consumption were not significantly associated with treatment group assignment. Although the degree of reduction in smoking achieved by study participants (means exceeding 80% for all 3 groups) appeared encouraging, neither biomarker of smoke exposure (ie, expired CO or saliva thiocyanate levels) declined during the trial, perhaps because of compensatory smoking (eg, deeper inhalation), reducing the inference of any health benefit related to smoking reduction. Alternatively, teens might have reported their cigarette consumption inaccurately. These results are consistent with findings from 2 adult studies, in which reductions in the numbers of cigarettes smoked were not accompanied by reductions in CO or thiocyanate concentrations[34] or reductions smaller than corresponding reductions in cigarette consumption were observed.[21] Active medication did not affect withdrawal scores in the current study, contrary to a previous study in which the patch group experienced a significant decrease in withdrawal scores, compared with placebo (data not shown).[15]

The nicotine patch and gum were well tolerated in this study and appeared safe. For the patch, this was similar to previous studies with adolescents,[12,13,15,16] and the adverse event profile was consistent with that from previous studies with adults.[38] Although we were not able to obtain adverse event data from trial dropouts, our clinical impression was that adverse events did not affect retention substantially. This is also suggested by the superior cessation out-

TABLE 3. Percentage Reductions in Measures of Smoking Among Completers, According to Treatment Group ($N = 52$)

	Patch	Gum	Placebo
Change in CPD, T11 − V1, %	−80.4 ± 7.52 ($N = 18$)*	−85.1 ± 5.13 ($N = 18$)*	−89.6 ± 4.98 ($N = 16$)*
Change in CO level, T11 − V1, %	10.5 ± 19.7 ($N = 18$)	37.7 ± 30.5 ($N = 18$)	30.8 ± 33.2 ($N = 16$)
Change in saliva thiocyanate level, T11 − V1, %	1.69 ± 26.6 ($N = 13$)	17.7 ± 23.7 ($N = 12$)	9.90 ± 13.5 ($N = 9$)

* Percentage change significantly different from 0 ($P < .05$) by paired t test.

come for the patch group, which reported the highest rate of side effects. We did not find any previously reported controlled studies of the gum among adolescents. Although not considered an adverse event, our clinical perception was that the aversive taste of the gum might have reduced compliance in the active-gum arm. Cotinine concentrations remained within the range from other similar studies, which suggests that the patch and gum remained safe for adolescents who continued to smoke. Although our attrition rate of 54% was high, it had been anticipated and was comparable to the 61% dropout rate recently reported for adolescent participants who attended trial visits at a research office.[15] Clearly, creative strategies are needed to retain adolescents in future medication trials that aim to treat tobacco dependence.

Several limitations of this study warrant attention. Only a small percentage of applicants who inquired via telephone were enrolled, compared with a previous randomized trial.[15] Stringent consumption and dependence eligibility criteria for this trial seem to have offset our otherwise liberal inclusion of participants with psychiatric disorders and drug and alcohol use. Alternatively, differences in sociodemographic characteristics in our trial, compared with the trial by Hanson et al,[15] might have affected eligibility for study participation. One example of this is our previously reported inadvertent exclusion of some black adolescents because of the their lower FTND scores.[39,40] The enrollment/randomization of only a small percentage of initial applicants is regrettable; however, as a first step, important information for developing and implementing other youth cessation research was obtained.[33] This was a rather lengthy study (3 months), with trial-related research procedures (eg, group therapy and questionnaire completion) exceeding standard practice-based cessation procedures at each visit. We wanted to obtain practical information pertaining to the use of both available over-the-counter modalities of NRT (of which only 1 was active) simultaneously. The external validity of this approach was based on the observations that both the patch and the gum are used commonly, often in combination, for cessation or reduction attempts.[37,38] The high degree of psychiatric comorbidity in this sample might have reduced cessation success.[41,42] Overall, gum compliance was suboptimal. Higher gum use in the placebo group might be attributable to increased use in a continued attempt to obtain an effect of the medication or, alternatively, less aversion for the placebo versus the active gum. Future studies with the nicotine gum among adolescents should test the recently available mint-flavored gum and provide increased, detailed, instructional support and rehearsal of gum use.

Because of the inclusion of highly addicted adolescents with substantial comorbidity, results from our sample can be extended to a broad range of settings in which adolescents might be seen for treatment of tobacco addiction and other clinical concerns. Although these results do not answer definitively the question of the efficacy of the patch or gum for treating adolescent smokers, the current findings lend empirical support to the US Public Health Service clinical practice guideline[11] for pediatricians, family practitioners, and other practitioners to prescribe or to recommend more consistently the nicotine patch, in addition to developmentally appropriate behavioral and counseling support, for adolescent smokers who are attempting to quit.

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