ORIGINAL INVESTIGATION

A Randomized Phase II Clinical Trial of High-Dose Nicotine Patch Therapy for Smokeless Tobacco Users

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Received April 12, 2013; accepted June 12, 2013

ABSTRACT

Introduction: Nicotine patch therapy has not been shown to be efficacious for increasing long-term (≥ 6 months) tobacco abstinence rates among smokeless tobacco (ST) users. Higher doses of nicotine patch therapy may be needed to increase tobacco abstinence rates in this population of tobacco users.

Methods: We randomized ST users who used ≥ 3 cans/pouches per week to either 8 weeks of high-dose nicotine patch therapy (42 mg/day) or matching placebo patch. Subjects were followed for 6 months after randomization.

Results: Fifty-two subjects were randomized. Compared with placebo, high-dose nicotine patch therapy was associated with significantly higher prolonged tobacco abstinence at end-of-treatment (44% vs. 22%, odds ratio [OR] = 2.7, $p = .050$) and 3 months (40% vs. 19%, OR = 2.9, $p = .047$). High-dose nicotine patch therapy was associated with significant weight gain attenuation among tobacco abstinence subjects at 3 months ($p = .013$) and 6 months ($p = .018$). Compared with placebo, high-dose nicotine patch therapy was associated with nonsignificantly lower nicotine withdrawal scores. Adverse events were not significantly increased with high-dose nicotine patch therapy.

Conclusions: High-dose nicotine patch therapy is safe and increases short-term tobacco abstinence rates among ST users who use ≥ 3 cans/pouches per week. High-dose nicotine patch therapy is associated with significant long-term attenuation of weight gain. Future studies to investigate the long-term efficacy of high-dose nicotine patch therapy and the comparative efficacy of this approach compared with standard nicotine patch doses for ST users seems warranted.

INTRODUCTION

In 2010, 8.9 million Americans (3.5%) ≥ 12 years of age reported past month use of smokeless tobacco (ST). Over the past decade, the tobacco marketplace has undergone significant transformation with the development and sale of newly branded ST products (Rogers, Biener, & Clark, 2010). The long-term use of ST used in the United States may be associated with an increased risk of death from cardiovascular disease and stroke (Henley, Thun, Connell, & Calle, 2005). A diverse armamentarium of pharmacotherapy needs to be available to treat ST users who wish to stop tobacco use.

In notable contrast to cigarette smokers, nicotine replacement therapy (NRT) has not been shown to increase long-term (≥ 6 months) tobacco abstinence rates in ST users (Ebbert, Montori, Erwin, & Stead, 2011). One reason for the lack of NRT efficacy among ST users may relate to the underdosing of nicotine replacement in this population of tobacco users. Experiments quantitating daily nicotine exposure during cigarette and ST use have shown that while maximal serum concentrations of nicotine are similar between users of cigarettes and

ST, the overall nicotine exposure may be twice as high in ST users as it is in cigarette smokers (Benowitz, Porchet, Sheiner, & Jacob, 1988).

Empirically derived nicotine patch dosing formulas have suggested that in the treatment of ST users, 42 mg/day of the nicotine patch should be started for individuals who use > 3 cans or pouches per week (Ebbert et al., 2004). Previous studies of higher doses of nicotine patch therapy among ST users have indeed demonstrated a dose–response relationship such that higher doses of the nicotine patch among ST users using ≥ 3 cans or pouches per week were associated with improved arousal and mood and decreased restlessness (Ebbert et al., 2007). However, the sample size of the 42 mg/day patch dose in this study was small ($n = 11$). The efficacy of the high-dose nicotine patch therapy (42 mg/day) for increasing both short-term and long-term tobacco abstinence rates among ST users remains uncertain.

In this study, we conducted a phase II clinical trial of 42 mg/day of the nicotine patch for increasing tobacco abstinence rates among ST users. We also sought to evaluate the potential impact of NRT on weight gain among ST users attempting to quit.

doi:10.1093/ntr/ntt097

Advance Access publication July 19, 2013

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METHODS

Study Design

We conducted a randomized, two-group, phase II clinical trial with an 8-week medication phase and follow-up for 6 months after randomization. Participants were randomized to receive either a daily nicotine patch dose of 42 mg or matching placebo patches. All participants received behavioral counseling. The study was conducted at Mayo Clinic (Rochester, MN) and enrollment took place between July 26, 2010, and June 13, 2012. The Mayo Institutional Review Board approved the study protocol prior to subject recruitment. An Investigational New Drug Application (IND) was obtained from the US Food and Drug Administration (FDA).

Study Population

ST users were recruited from the local community using press releases and advertising. Participants were eligible for inclusion if they (a) were between 18 and 55 years of age; (b) reported daily ST use for the past 12 months; (c) identified ST as their primary tobacco product; (d) used an average of ≥ 3 cans/pouches per week; (e) were in general good health as determined by medical history and screening physical examination; and (f) had been provided with, understood, and signed the informed consent. Potential participants were excluded from study participation if they: (a) were currently (past 30 days) using any other behavioral or pharmacologic tobacco dependence treatment program; (b) were currently pregnant or lactating; (c) had unstable angina, myocardial infarction, or coronary angioplasty within the past 3 months; (d) had a history of arrhythmia or an abnormal tracing on the baseline electrocardiogram; (e) had a blood pressure of $>140/90$ or a pulse of more than 110 beats per minute; (f) had a history of severe skin allergies or dermatoses; (g) had a history of intolerance to nicotine patches; (h) had another member of their household already participating in this study; (i) were taking a medication known to interact with nicotine; or (j) were taking any prescription medication for depression or asthma.

Screening and Enrollment

Potential participants satisfying a subset of study eligibility criteria over the phone were invited to attend a study visit at which time the study was described, informed consent was obtained, and a medical screening and physical examination were completed.

Blinding and Randomization

Study personnel who did not have any subject contact placed the appropriate study patch according to subject identification numbers into labeled plastic bags. At enrollment, a subject was assigned the next sequential subject identification number. All study medication was labeled and dispensed according to subject identification ensuring that treatment assignment remained concealed to the subject, investigator, and all study personnel having subject contact. Following completion of the informed consent, subjects were randomly assigned in a 1:1 ratio to the treatment condition using a computer-generated randomization sequence with a block size of two.

Treatment and Control Conditions

At randomization, subjects were assigned to a daily dose of 42 mg of the nicotine patch or matching placebo patches. Subjects were instructed to apply two 21 mg patches or two identical placebo patches in the morning on their target quit date (TQD). Patches were to be worn on different anatomical sites each day for a total of 8 weeks. Nicotine patches were given for 8 weeks because: (a) high-dose nicotine patch studies with cigarette smoker have used 8 weeks of therapy (Fredrickson et al., 1995; Jorenby et al., 1995); (b) meta-analyses have observed that no differences exist in efficacy between nicotine patch studies with longer (12 weeks) and shorter durations (3 weeks) in cigarette smokers (Stead et al., 2012); and (c) it is consistent with the recommendations of the US Public Health Service Guidelines, which suggests that the nicotine patch should be used for 8 weeks (Fiore et al., 2008). Subjects in the active group wore two 21 mg nicotine patches/day for 6 weeks and one 21 mg patch/day for 2 weeks. Subjects in the placebo group wore two identical-appearing placebo patches for 6 weeks and one placebo patch/day for 2 weeks.

The study was composed of eight clinical research unit study visits, four of which occurred during the drug treatment phase. Research study visits lasted an average of 30–45 min. During the medication phase, participants attended four study visits during which individualized behavioral interventions sessions were provided, each of which were a minimum of 10 min in duration. Counseling did not last more than 15 min. Goals of these sessions were to assist with initial tobacco abstinence and to provide relapse prevention tools. Interventions were delivered by research staff not involved with the collection of baseline and outcome measures who were trained on the intervention by an investigator. Behavior change strategies incorporated many of the cognitive behavioral self-management strategies recommended by Marlatt (Marlatt, Parks, & Witkiewitz, 2002) and Ockene et al., (2000) including making a personal contract to quit, getting support, identifying and building coping strategies for high risk situations, dealing with nicotine withdrawal, understanding and managing negative cognitions, and knowing what to do in the event that lapses occur. Participants received a copy of a self-help manual (i.e., “Skip the Dip, Lose the Chew”) developed by our clinical and research team specifically for ST users and used in our previous ST studies (Dale et al., 2002, 2007; Ebbert et al., 2007). Subjects were instructed to read through the manual and bring in questions they may have for the next visit.

Participants who completed the 8-week medication phase were followed up at 3 and 6 months after randomization. Adverse events and concomitant tobacco dependence treatments were recorded. A urine specimen was collected for biochemical confirmation of tobacco use status at 3 and 6 months after randomization among participants self-reporting tobacco abstinence.

Measures

Baseline measures included a demographics, tobacco use history, and the Fagerström Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST) (Ebbert, Patten, & Schroeder, 2006). Tobacco abstinence was determined by self-report at each visit and was biochemically confirmed at 3 and 6 months. Cotinine is the traditional measurement for adjudication of self-reported tobacco abstinence (Benowitz et al., 2002), but cotinine cannot be

used to biochemically validate tobacco abstinence during use of NRT. Since NRT does not contain the tobacco alkaloid anabasine while tobacco does, urinary anabasine has been proposed as a biomarker of tobacco consumption that could differentiate tobacco users and nonusers who use NRT (Jacob, Yu, Shulgin, & Benowitz, 1999; Moyer et al., 2002). We adjudicated self-reported abstinence with a urinary anabasine concentration of <2 ng/ml as has been used in our previous investigations (Ebbert, Severson, Croghan, Danahey, & Schroeder, 2009).

Tobacco Abstinence

Tobacco abstinence endpoints of interest included point prevalence and prolonged tobacco abstinence at end-of-treatment (8 weeks) and at 3 and 6 months. Point-prevalence tobacco abstinence was defined as self-reported 7-day tobacco abstinence confirmed by a urinary anabasine <2 ng/ml. Participants who met criteria for biochemically confirmed 7-day point-prevalence abstinence at a given visit were defined as meeting criteria for prolonged abstinence if they submitted negative responses to both of the following questions: "Since 14 days after your target quit date, have you used any tobacco on each of 7 consecutive days?" and "Since 14 days after your target quit date, have you used any tobacco on at least one day in each of 2 consecutive weeks?" (Hughes et al., 2003). If a participant missed a visit, they were classified as using tobacco at that visit.

Nicotine Withdrawal and Tobacco Craving

Subjects were asked to keep a daily diary that included the Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986, 1998) replacing the item "desire to smoke" with "desire to use tobacco." We have used this diary in previous studies with ST users (Ebbert et al., 2009; Ebbert, Croghan, Severson, Schroeder, & Hays, 2011; Ebbert, Severson, Croghan, Danahey, & Schroeder, 2013).

Adverse Events

Self-reported adverse events were documented, addressed according to a safety management protocol, and followed through to resolution.

Statistical Analyses

The sample size for this study was determined for the primary endpoint of 7-day point-prevalence tobacco abstinence at the end of the medication phase. Based on our previous experience treating ST users, we hypothesized conservative end-of-medication abstinence rates of 33% for placebo and 65% for the high-dose nicotine patch therapy group (Ebbert et al., 2007). Using these assumptions, we determined that a total sample size of 60 (30 per group) would provide statistical power (one-tailed, $\alpha = .05$) of 80% to detect the hypothesized difference between groups.

All analyses were performed using an intention-to-treat approach with subjects analyzed according to randomized treatment. Tobacco abstinence endpoints at end-of-treatment, 3 months, and 6 months were analyzed separately using logistic regression. The results of these analyses were summarized by presenting the point estimate and 90% confidence interval for the odds ratio. For subjects who met criteria for prolonged tobacco abstinence, weight change from baseline at

end-of-treatment and 6 months was compared between treatment groups using the two-sample *t* test. A composite nicotine withdrawal score was calculated as the mean of the following eight items on the daily diary: anger, irritability, or frustration; anxiety or nervousness; difficulty concentrating; impatience; restlessness; hunger; awakening at night; and depression. An additional item, "desire to use tobacco" was analyzed separately as a measure of tobacco craving. Baseline scores were calculated using data from all diaries completed prior to the start of medication. Composite nicotine withdrawal scores and craving scores obtained for the first 2 weeks after the TQD were analyzed as change from baseline using Generalized Estimating Equations to accommodate a varying number of observations for each individual and take into account the clustering of repeated measures within individuals. For these analyses, data were included for each subject up to the day they first reported using tobacco following the TQD. In addition to treatment, a continuous variable corresponding to the days since the TQD was included in the analysis along with the treatment-by-time interaction effect. Medication adherence, defined as the number of patches used divided by the total number of patches prescribed for the 8-week treatment phase, was compared between groups using the rank sum test, and the frequency of adverse events was compared between groups using the Fisher exact test. For tobacco abstinence endpoints, a one-tailed *p* value $\leq .05$ was considered statistically significant. For all other comparisons, two-tailed *p* values are reported.

RESULTS

Participants

Of 130 individuals screened, 62 consented to the study and 52 were randomized to treatment (Figure 1; Table 1). Enrollment was terminated early after the 52nd subject was randomized due to recruitment and difficulty in securing additional placebo patches. Fifteen subjects (4 high-dose nicotine patch and 11 placebo) discontinued the study prior to the end of medication phase. Most of these subjects (three high-dose nicotine patch and 9 placebo) reported using tobacco at the last study visit they attended prior to discontinuing the study. For all randomized subjects, the median medication adherence was 93% for the high-dose nicotine patch group and 61% for placebo ($p = .280$). Among subjects who did not discontinue the study prior to the end of the medication phase, the median medication adherence was 98% for the high-dose nicotine patch group and 93% for placebo ($p = .778$).

Tobacco Abstinence

High-dose nicotine patch therapy was associated with higher tobacco abstinence rates at end-of-treatment and 3 months (Table 2). Tobacco abstinence rates were nonsignificantly higher in the high-dose nicotine patch group at 6 months.

Nicotine Withdrawal and Tobacco Craving

Although not statistically significant, the mean composite nicotine withdrawal score was observed to be higher in the placebo group for the first week following the TQD (treatment: estimate = -0.08 , $SE = 0.23$, $p = .74$; time: estimate = -0.03 , $SE = 0.01$, $p = .029$;

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Figure 1. CONSORT diagram.

treatment-by-time: estimate = -0.004 ; $SE = 0.02$, $p = .85$) (Figure 2). Similar results were found for craving (treatment: estimate = -0.30 , $SE = 0.39$, $p = .45$; time: estimate = -0.14 , $SE = 0.03$, $p < .001$; treatment-by-time: estimate = 0.03 ; $SE = 0.05$, $p = .52$).

Weight Gain

Among subjects who met criteria for prolonged tobacco abstinence at end-of-treatment, the mean ($\pm SD$) weight change from baseline to end-of-treatment was significantly less in the high-dose nicotine patch group compared with placebo (2.4 ± 1.7 vs. 4.9 ± 1.8 kg, $p = .013$). A similar reduction in post-cessation weight gain from baseline to 6 months was observed among subjects who met criteria for prolonged abstinence at 6 months (1.4 ± 2.9 vs. 5.6 ± 2.0 kg, $p = .018$). In order to explore this further, we performed an analysis comparing the change in weight from week 8 to 6 months among subjects who met criteria for prolonged abstinence at 6 months. From this analysis, the estimated treatment effect was -1.7 kg, suggesting less weight gain in the nicotine group, but this difference was not statistically significant ($p = .31$).

Adverse Events

A total of 11 subjects (7 nicotine and 4 placebo) reported 12 adverse events considered to be possibly, probably, or definitely related to the study medication. These included patch site reaction (2 nicotine and 2 placebo), nausea (2 nicotine and 0 placebo), anxiety (1 nicotine and 0 placebo), diarrhea (0 nicotine and 1 placebo), dizziness (1 nicotine and 0 placebo), irritability (0 nicotine and 1 placebo), itching (1 nicotine and 0 placebo), and sleep disturbance (0 nicotine and 1 placebo). No serious adverse events were observed.

DISCUSSION

The results of our phase II clinical trial suggest that high-dose nicotine patch therapy increases tobacco abstinence among ST users at end-of-treatment and 3 months. High-dose nicotine patch therapy attenuated weight gain at 3 and 6 months, decreased nicotine withdrawal, and was not associated with higher rates of adverse events.

Table 1. Baseline Demographics of Smokeless Tobacco (ST) Users in a Phase II Randomized Clinical Trial of High-Dose Nicotine Patch Therapy^a

Characteristic	42 mg/day nicotine patch (N = 25)	Placebo patch (N = 27)
Age, y	39.2 ± 9.1	35.3 ± 9.5
Male, n (%)	25 (100)	27 (100)
Race/ethnicity, n (%)		
Caucasian, non-Hispanic	23 (92)	26 (96)
Caucasian, Hispanic	2 (8)	1 (4)
Marital status, n (%)		
Married/living as married	19 (76)	17 (63)
Never married	3 (12)	8 (30)
Separated/divorced	3 (12)	2 (7)
Highest level of education, n (%)		
High school graduate	3 (12)	3 (11)
Some college	11 (44)	16 (59)
College graduate	11 (44)	8 (30)
FTND-ST	5.6 ± 1.7	5.8 ± 1.3
ST used per week, cans/pouches	4.6 ± 1.8	4.0 ± 1.3
Regular ST use, years	19.2 ± 9.4	16.8 ± 10.5
Current use of other tobacco products, n (%)	0 (0)	0 (0)
Close friends who use ST, n (%)	19 (76)	18 (67)
Longest duration of previous abstinence, n (%)		
≤ 7 days	10 (40)	11 (41)
8–28 days	5 (20)	3 (11)
1–6 months	4 (16)	4 (15)
> 6 months	6 (24)	9 (33)
Confidence in not using ST one year from now, n (%)		
Not at all confident	0 (0)	0 (0)
Not very confident	0 (0)	1 (4)
Somewhat confident	12 (48)	13 (48)
Very confident	13 (52)	10 (37)
Completely confident	0 (0)	3 (11)
Contemplation ladder	8.3 ± 1.3	8.5 ± 1.2
Alcoholic drinks in last 7 days, n (%)		
None	5 (20)	5 (19)
1–3	4 (16)	6 (22)
4–6	6 (24)	7 (26)
7–12	4 (16)	4 (15)
13 or more	6 (24)	5 (19)
Binge drinking episodes ^b in last 30 days		
None	8 (32)	12 (44)
1–3	11 (44)	7 (26)
4–6	4 (16)	6 (22)
7 or more	2 (8)	2 (7)

Note. FTND-ST = Fagerström Test for Nicotine Dependence-Smokeless Tobacco.

^aData are presented as mean ± SD or n (%) as indicated.

^bBinge drinking episodes were defined as five or more drinks on a single occasion.

Our data support previous studies suggesting that nicotine patch therapy increases short-term tobacco abstinence in ST users. But in all previous clinical trials with ST users, regular doses of the nicotine patch failed to increase long-term (≥ 6 months) abstinence rates. In a study of 410 adult ST users randomized to 15 mg/16 hr nicotine patch or placebo for 6 weeks, the nicotine patch did not increase the biochemically confirmed point-prevalence ST abstinence at 6 months although it did prevent relapse as demonstrated by survival analyses (Howard-Pitney, Killen, & Fortmann, 1999). The nicotine patch also increased abstinence rates at 3 months. In another study incorporating a 2 × 2 factorial design, 402 ST users were

randomized to 21 mg/day of the nicotine dose or placebo and mint snuff (i.e., non-tobacco, non-nicotine ST substitute) versus no mint snuff for 10 weeks (Hatsukami et al., 2000). Subjects received nicotine patch therapy or placebo for 6 weeks and were tapered using 14 mg/day for 2 weeks and 7 mg/day for 2 weeks. Significant differences in continuous ST abstinence rates were observed only at the end of 10 weeks of treatment. Our data suggest the effect of high-dose nicotine patch therapy may endure to 6 months, but our results were not statistically significant.

The current investigation extends previous work evaluating high-dose nicotine patch therapy for ST users (Ebbert et al., 2004, 2007). In a previous study of 24 ST users admitted

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Table 2. Abstinence Outcomes of Smokeless Tobacco Users in a Phase II Randomized Clinical Trial of High-Dose Nicotine Patch Therapy^a

	42 mg/day nicotine patch <i>N</i> = 25 (%)	Placebo patch <i>N</i> = 27 (%)	Odds ratio		<i>p</i> value ^b
			Estimate	(90% CI)	
End-of-treatment (week 8)					
Point-prevalence abstinence	11 (44)	6 (22)	2.7	(1.0, 7.5)	0.050
Prolonged abstinence	11 (44)	6 (22)	2.7	(1.0, 7.5)	0.050
3 months					
Point-prevalence abstinence	12 (48)	5 (19)	4.1	(1.4, 11.6)	0.014
Prolonged abstinence	10 (40)	5 (19)	2.9	(1.0, 8.4)	0.047
6 months					
Point-prevalence abstinence	11 (44)	7 (26)	2.2	(0.8, 6.0)	0.087
Prolonged abstinence	8 (32)	5 (19)	2.1	(0.7, 6.1)	0.133

Note. CI = confidence interval.

^aSubjects met criteria for point-prevalence all tobacco abstinence if they reported not using any tobacco in the last 7 days and had a urinary anabasine of <2.0 ng/ml. To meet criteria for prolonged abstinence, subjects had to meet criteria for 7-day point-prevalence abstinence and also report not using tobacco for 7 consecutive days nor at least once each week on two consecutive weeks, since 2 weeks following their target quit date. In all cases, subjects with missing information were assumed to be using tobacco.

^bOne-tailed, chi-square test.

Figure 2. Composite nicotine withdrawal of smokeless tobacco users in a randomized clinical trial of high-dose nicotine patch therapy.

to an 8-day residential program, nicotine patch doses up to 63 mg/day were prescribed (Ebbert et al., 2004). Dose adjustments were made based on baseline serum nicotine concentrations. The median nicotine “percent replacement” ([serum nicotine concentration on nicotine patch ÷ serum nicotine concentration during ad lib ST use] × 100%) was 86.6% on an average nicotine patch dose of 43.2 mg/day ± 13.9 (SD). In another study, 42 adult ST users who used ≥3 cans/pouches per week were randomized to nicotine patch doses of 21, 42, or 63 mg/day or placebo (Ebbert et al., 2007).

Using an electronic diary to conduct ecological momentary assessments, negative affect, decreased arousal, attention disturbance, and restlessness were assessed. A dose–response relationship was observed such that higher nicotine patch doses were associated with less decreased arousal ($\chi^2 = 6.87$, $p = .009$), less negative affect ($\chi^2 = 3.85$, $p = .05$), and less restlessness ($\chi^2 = 3.90$, $p = .048$) in the first week after the TQD. During the second week, higher nicotine patch doses were associated with less impairment in arousal ($\chi^2 = 6.77$, $p = .009$). In this study, we observed that the nicotine

withdrawal symptoms were lower in the high-dose nicotine patch group than in the placebo group. However, we were not using ecological assessments, which provide richer withdrawal data, and we may have been underpowered to detect a statistically significant effect.

We observed that weight gain was significantly attenuated among ST users. Subjects receiving high-dose nicotine patch therapy gained an average of 2.4 kg at 3 months and 1.4 kg at 6 months. Weight gain was similar to cigarette smokers receiving NRT who gain a mean of 2.3 kg at 3 months (Aubin, Farley, Lycett, Lahmek, & Aveyard, 2012). However, the weight gain in this study was less than that observed among smokers at 6 months (3.6 kg). When we analyzed the change in weight from week 8 to 6 months among subjects who met criteria for prolonged abstinence at 6 months, the difference between the nicotine patch and placebo groups was not statistically significant. Furthermore, the 95% confidence interval for this effect had an upper bound of +1.8 kg, which is consistent with what might typically be expected after stopping medication. No previous nicotine patch studies have evaluated the effect of NRT on post-cessation weight gain among ST users. However, in a previous study of ST users, bupropion SR was observed to attenuate weight gain at 3 months compared with placebo (1.7 ± 2.9 kg for bupropion SR vs. 3.2 ± 2.7 kg for placebo; $p = .005$). Twenty-five percent of male cigarette smokers are weight concerned (Clark et al., 2004), but no data exist regarding the degree to which male ST users are weight concerned. Both high-dose nicotine patch therapy and bupropion SR may be effective for prevention of weight gain with ST cessation.

The major strength of our study was the randomized, controlled clinical trial design. Our major limitation was our small sample size. Another potential limitation of our study is in the assessment of prolonged tobacco abstinence. Wording for the question was derived from published guidelines (Hughes et al., 2003), but may have been difficult for patients to understand. Difficulty in understanding this question should not have affected groups differentially (i.e., the same amount of erroneous reporting would be expected to occur in both groups).

High-dose nicotine patch therapy is safe and effective for increasing short-term tobacco abstinence and for attenuating both short- and long-term post-cessation weight gain among ST users who use ≥ 3 cans or pouches per week. Future investigations should investigate the long-term (≥ 6 months) efficacy of high-dose nicotine patch therapy with a larger sample size and the comparative efficacy of this approach to standard dose nicotine patch therapy.

FUNDING

This study was supported by National Institutes of Health grant CA 140125 (JOE).

DECLARATION OF INTERESTS

JOE reports a grant from NIH during the conduct of the study. JOE also received grants from Pfizer and personal fees from GlaxoSmithKline for studies not related to the study reported. RDH reports grants from NIH and Pfizer outside the submitted work. ITC and DRS report no conflicts of interest.

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