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Effect of Nicotine Replacement Therapy on Stress and Smoking Behavior in Surgical Patients

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Background: **Many surgical patients are dependent on nicotine. Smoke-free policies in healthcare facilities mandate abstinence from smoking, which could contribute to psychological stress in the perioperative period. The authors tested the hypothesis that nicotine replacement therapy decreases psychological stress in cigarette smokers scheduled to undergo elective surgery and determined whether nicotine replacement therapy affects postoperative smoking behavior, even when not specifically prescribed to promote abstinence.**

Methods: **In this double-blind, placebo-controlled trial, 121 smokers, of whom 116 received a study intervention, were randomly assigned to receive either active (nicotine-containing) or placebo patches, beginning on the morning of surgery and continuing for up to 30 days after discharge from the hospital. Outcomes included the Perceived Stress Score, the Nicotine Withdrawal Score, and subject self-report of smoking behavior.**

Results: **The Perceived Stress Score and the Nicotine Withdrawal Score did not change significantly from baseline over the immediate perioperative period and did not differ between active or placebo patch groups (all $P > 0.19$). The percentage of placebo *versus* active patch subjects reporting 7-day abstinence at 30 days postoperatively (30% *vs.* 39%; $P = 0.29$) did not differ significantly between groups. At 30 days postoperatively, subjects in both groups significantly reduced their cigarettes smoked per day from baseline, but those receiving active patches reported a greater decrease (a mean decrease of 11 ± 11 *vs.* 15 ± 7 cigarettes/day in placebo and active groups; $P = 0.045$).**

Conclusion: **Routine nicotine replacement therapy is not indicated in smokers undergoing surgery for the purposes of managing nicotine withdrawal and stress but can modify some aspects of postoperative smoking behavior.**

MILLIONS of patients undergoing surgery each year are addicted to nicotine. Because of smoke-free policies in healthcare facilities, surgical patients cannot maintain their usual patterns of nicotine use while in these facilities and could develop symptoms of nicotine withdrawal. A variety of systems to administer nicotine can help smokers to manage withdrawal during abstinence from cigarettes,[1] including patches, gum, lozenges, inhalers, and nasal spray, but hospitalized smokers use nicotine replacement therapy (NRT) infrequently.[2,3] Because many smokers view cigarettes as a tool to attenuate stress,[4,5] NRT could assist smokers in managing the considerable psychological stresses associated with surgery. Perioperative NRT could also contribute to a reduced smoking rate (including abstinence) in the postoperative period. However, there is little published experience regarding the use of NRT in surgical patients, and some have raised concerns that NRT could be harmful in this setting.[6–8]

Our overall goal was to examine the role of NRT in the perioperative period. The primary aim was to test the hypothesis that NRT decreases psychological stress in cigarette smokers scheduled to undergo elective surgery, using a randomized, double-blind, placebo-controlled study design. Secondary aims were to assess safety, adverse effect profile, and patient compliance with NRT in the perioperative period and to determine whether the application of NRT to these patients for up to 30 days after surgery affects postoperative smoking behavior, even when not specifically prescribed to promote abstinence.

Materials and Methods

Recruitment

After approval from the Mayo Clinic Institutional Review Board (Rochester, Minnesota) was obtained, subjects were recruited from patients evaluated at the Mayo Clinic Rochester Preoperative Evaluation Center in preparation for elective surgery. Approximately 20% of adult patients undergoing surgery at Mayo Clinic Rochester are seen in this facility (other surgical patients are evaluated preoperatively using other mechanisms), permitting sampling of a general surgical population. Eligibility criteria included age of 18 yr or older and a history of smoking at least 1 cigarette/day during the past week, with an average consumption of 10 or more cigarettes/day during the past 30 days. Subjects were told that the purpose of the study was to determine whether nicotine patches would help them cope with not being able to smoke around the time of surgery. The patches were not characterized as an aid to help them permanently quit smoking. Written informed consent was obtained.

Procedure

After enrollment, subjects were randomly assigned to receive either active nicotine patches or placebo patches,

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which could not be distinguished by appearance. Randomization was performed using two stratification factors: baseline smoking rate (10–20, 21–40, or ≥ 41 cigarettes/day) and anticipated type of surgery (inpatient *vs.* outpatient). For each stratum, a randomization schedule was generated by the Mayo Division of Biostatistics using a block size of four. Using these randomization schedules, study patches were packaged according to strata-specific subject identification numbers by personnel without subject contact. At the time of enrollment, group assignment was determined by assignment of the next sequential subject identification number for the appropriate strata. All parties were blinded to treatment assignment.

The dosing of patches was based on the average number of cigarettes per day, using a regimen validated in previous studies.[9,10] For subjects randomly assigned to active patch, those smoking 10–20 cigarettes/day received a patch dose of 21 mg/day, those smoking 21–40 cigarettes/day received a dose of 35 mg/day (requiring two patches), and those smoking more than 40 cigarettes/day received a dose of 42 mg/day (requiring two patches). Active (equivalent to Nicoderm CQ; GlaxoSmithKline, Research Triangle Park, NC) and placebo patches were provided by GlaxoSmithKline. At enrollment, subjects were instructed regarding proper patch use, including procedures for site rotation and treatment of local irritation. Instructions were repeated preoperatively on the morning of surgery, and the first patch was applied by study personnel before the subject left the preoperative area. Study personnel confirmed proper patch application throughout hospitalization, answering any subject questions regarding patch use. At the time of discharge from the hospital, subjects were given a 30-day supply of patches. No behavioral counseling or other interventions were provided to help subjects maintain abstinence from cigarettes.

Assessments

Subjects were assessed twice preoperatively: at the time of enrollment in the Preoperative Evaluation Center (initial assessment) and on the morning of surgery (preoperative assessment). Postoperatively, assessments included the day of surgery (defined as postoperative day [POD] 1) and the time of discharge from the hospital (for outpatients), or on the hospital floor after discharge from the postanesthesia care unit on the day of surgery (for inpatients). Assessments were also performed at 2, 3, 8, 30, and 180 days postoperatively. Postoperative assessments were performed in person (if the subject was still in the facility) or by telephone (if the subject had been discharged). Assessments were performed only if subjects were sufficiently awake to respond appropriately and were administered privately by study personnel using an interview format. Components of these assessments included the following.

Initial Measures. Demographic information and comorbidity (defined according to standard criteria[11]) were abstracted from the medical record. A current smoking history was obtained, including the Fagerström Test for Nicotine Dependence[12] and three questions assessing stage of change as previously adapted to the perioperative period.[13] If subjects answered affirmatively to the question "Is it your plan to stay quit once you leave the hospital?," they were classified as being in the "action" stage. If they answered negatively, but answered affirmatively to the question "Do you plan to initiate a serious quit attempt within 30 days after you leave the hospital?," they were classified as being in the "preparation" stage. If they answered negatively, but answered affirmatively to the question "Do you plan to initiate a serious quit attempt within 6 months after you leave the hospital?," they were classified as being in the "contemplation" stage. If they answered negatively, they were classified as being in the "precontemplation" stage.

Other Measures. The Minnesota Nicotine Withdrawal Questionnaire[14,15] was used to assess nicotine withdrawal symptoms for the past 24-h period, producing a composite Nicotine Withdrawal Score (NWS). The 10-item Perceived Stress Scale (PSS)[16–18] assessed psychological stress, with questions asked in relation to experiences within the past 24 h, similar to our previous work.[13] Patients were also asked to rate their overall current stress on a subjective 11-point scale, with 0 representing no stress and 10 representing the worst stress imaginable, referred to as the Numerical Stress Score (NSS).[13] A Numerical Pain Score (NPS)[19,20] for current pain at rest (from 0 [representing no pain] to 10) was also obtained.

Self-reported smoking behavior was ascertained for the time since the last assessment. Expired carbon monoxide concentrations were obtained immediately preoperatively with a handheld device to confirm recent smoking status. Side effects possibly related to NRT were specifically queried, and all adverse perioperative events were noted. Adherence to patch use was assessed by subject self-report.

Data Analysis

The sample size was determined for the primary endpoint of perceived stress, assuming an SD for PSS similar to that reported from a sample of US adults.[17] For continuous endpoints, a sample size of 60 per group provides power (two tailed, $\alpha = 0.05$) of approximately 80% to detect a difference between groups of 0.5 SD units.

Data collected during the immediate perioperative period (defined as from the morning of surgery through POD 8) for the NWS, PSS, NSS, and NPS were analyzed using PROC MIXED (version 8.2 of the SAS System for Unix; SAS Institute Inc., Cary, NC). For these models, a first-order autoregressive structure was used to model the covariance of repeated measures within individuals.

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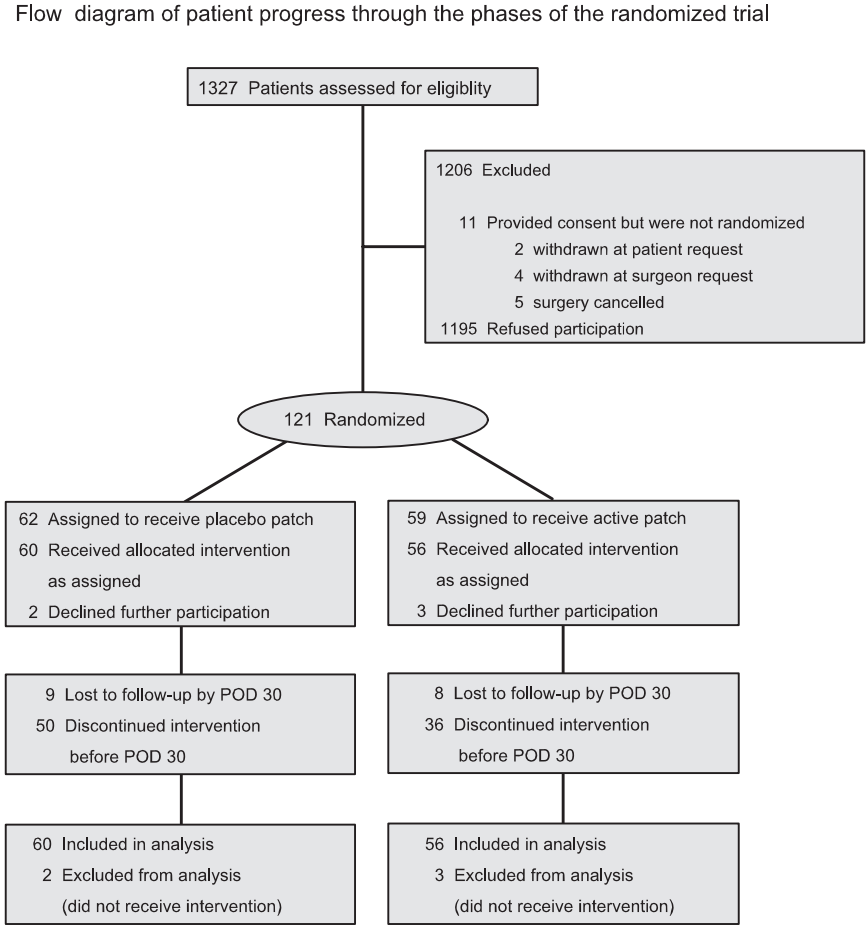

Fig. 1. Flow diagram. POD = postoperative day.

Because of a skewed distribution, the analysis of PSS was performed using the square root of PSS as the dependent variable. To supplement these analyses, groups were compared separately at each time point using the rank sum test for PSS and the two-sample *t* test for NWS, NSS, and NPS. The proportions of subjects reporting 7-day point-prevalence abstinence from smoking at 30 and 180 days after surgery were compared between groups using the chi-square test, and at each time point, the changes in smoking rate from baseline were compared between groups using the rank sum test. In all cases, subjects with missing abstinence information were assumed to be smoking at the same rate reported at the initial assessment. In addition, the time to smoking relapse and duration of patch use during the first 30 days after discharge from the hospital were compared between groups using the log rank test. To assess for potential differences in treatment effects based on length of hospital stay (LOS), the analyses of PSS, NSS, and NWS were repeated including LOS as a covariate. For these analyses, LOS was treated as a categorical variable (0 days [outpatient surgery], 1 or 2 days, 3 or more days), and the LOS-by-treatment interaction effect was assessed to determine whether there were differential treatment effects. Similar analyses were performed using proportional hazards regression to assess differential treatment effects for the secondary outcomes of time to relapse to smoking and duration of patch use. Other outcomes were compared between groups using the chi-square test or Fisher exact test, as indicated. In all cases, two-sided tests were used; $P \leq 0.05$ denoted statistical significance.

Results

Study Sample

Recruitment occurred from October 2001 to February 2004 (inclusive). During this time, 15,981 subjects were evaluated in the preoperative center. Of these subjects, 1,327 (8.3%) met initial eligibility criteria. Of those meeting criteria, 132 (10%) provided consent and were enrolled, and 121 (9.1%) were randomized (fig. 1). Five subjects (2 placebo, 3 active) declined further participation after randomization but before patch application; this report presents data from the 116 subjects who received patches. Fifteen subjects (7 placebo, 8 active) underwent outpatient procedures, with the remainder admitted to the hospital after surgery. Subjects in the active group were significantly older and less likely to have a history of lung disease; otherwise, demographic characteristics did not differ (table 1). The distribution of

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Table 1. Subject Characteristics

Characteristic	Placebo (n = 60)		Active (n = 56)	
	Mean ± SD	Median (range)	Mean ± SD	Median (range)
Sex, n (%)				
Male	31 (52%)		28 (50%)	
Female	29 (48%)		28 (50%)	
Age, yr	47.1 ± 13.4	47.5 (18–80)	52.2 ± 9.9	52 (26–73)
BMI, kg/m^2	29.4 ± 7.6	28.0 (17.7–55.5)	28.3 ± 6.9	26.0 (19.8–57.8)
Received an inpatient procedure, n (%)	53 (88%)		48 (86%)	
Days hospitalized	3.1 ± 3.6	2 (0–25)	3.1 ± 2.4	3 (0–10)
IDDM, n (%)	1 (2%)		2 (4%)	
Hypertension, n (%)	15 (25%)		14 (25%)	
CAD, n (%)	4 (7%)		4 (7%)	
Past MI, n (%)	5 (8%)		3 (5%)	
Asthma/COPD, n (%)	9 (15%)		2 (4%)	

Treatment groups were compared using a chi-square test for categorical variables and a rank sum test for continuous variables. Comorbid conditions were defined according to previously reported criteria.[11] Age and asthma/chronic obstructive pulmonary disease (COPD) differed between groups ($P = 0.02$ and 0.04, respectively).

BMI = body mass index; CAD = coronary artery disease; IDDM = insulin-dependent diabetes mellitus; MI = myocardial infarction.

surgical procedures was similar between the two groups (table 2).

Smoking behavior at enrollment did not differ significantly between groups (table 3). Overall, 48% of subjects were highly dependent on nicotine, defined as a Fagerström Test for Nicotine Dependence score of greater than 6. Preoperatively, most (85%) were classified as being in the action stage of change (*i.e.*, planned to maintain abstinence after surgery).

Stress, Nicotine Withdrawal, and Pain

At the time of the initial assessment in the Preoperative Evaluation Center, the NWS, PSS, and NSS did not significantly differ between groups (table 4). Both the NWS and the PSS were relatively constant during the first week after surgery, with no significant time or treatment effects detected. Similar findings were observed in analyses that adjusted for LOS. The NSS significantly decreased over time by an amount that did not depend on treatment assignment. The NPS was not significantly different between groups at the time of initial assessment (4.8 ± 3.1 and 4.7 ± 3.2 in the placebo and active groups, respectively). The NPS did not differ between treatment groups; however, as expected, the NPS increased immediately postoperatively and then declined (fig. 2).

Table 2. Surgical Procedures

Procedure	Placebo (n = 60)	Active (n = 56)
Orthopedic	22 (37)	21 (38)
Intraabdominal	9 (15)	12 (21)
Spine	10 (17)	8 (14)
Genitourinary	5 (8)	5 (9)
Otorhinolaryngologic	7 (12)	3 (5)
Gynecologic	3 (5)	4 (7)
Other	4 (7)	3 (5)

Data are presented as n (%).

Smoking Behavior and Patch Use

Most subjects continued to smoke until immediately before admission to the hospital (table 3). All subjects except one reported maintaining smoking abstinence during hospitalization. The proportions of subjects reporting continuous or current smoking abstinence at POD30 or POD180 did not differ between groups (table 5). Subjects receiving active patch tended to relapse to smoking at a later time (medians of 2.5 and 12.5 days after discharge for the placebo and active groups, respectively), but this difference was not significant ($P = 0.22$). However, when the analysis was repeated with LOS included as a covariate, there was evidence of a treatment-by-LOS interaction ($P = 0.05$), indicating that treatment effect depended on LOS (fig. 3). Subsequent analyses performed separately for LOS subgroups indicate that active patch was more effective at delaying relapse to smoking in those with shorter hospital stays ($P = 0.002$ for outpatients, $P = 0.08$ for LOS of 1 or 2 days, $P = 0.69$ for LOS of 3 or more days). At POD30, although both groups had significantly reduced their cigarette consumption compared with preoperative rates, those receiving active patches experienced a significantly greater decrease in cigarettes smoked per day (table 5). This difference disappeared by POD180, although cigarette consumption was still decreased compared with preoperative rates.

Thirty-seven subjects (18 in the placebo group and 19 in the active group; $P = 0.69$) reported at least one adverse event postoperatively. Of the 54 events reported in these 37 subjects, 35 (15 in the placebo group and 20 in the active group) could possibly have been related to nicotine therapy (*e.g.*, dizziness, vivid dreams, nausea).

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Table 3. Preoperative Smoking Behavior

Characteristic	Placebo (n = 60)		Active (n = 56)	
	n	Number (%)	n	Number (%)
Cigarettes per day, mean ± SD (median, range)	60	23.5 ± 9.2 (20, 10–60)	56	22.8 ± 9.3 (20, 10–42)
FTND score	58		52	
< 6		32 (55%)		25 (48%)
≥ 6		26 (45%)		27 (52%)
Hours since last cigarette at preoperative assessment, median (range)	59	1.4 (0.2–25.1)	55	1.5 (0–48.5)
Expired carbon monoxide at preoperative assessment, ppm, mean ± SD	58	18.0 ± 10.4	55	15.3 ± 9.4
Number of past cessation attempts	59		52	
0		8 (14%)		11 (21%)
1		14 (24%)		8 (15%)
≥ 2		37 (63%)		33 (64%)
Most recent cessation attempt*	51		40	
Within the past year		13 (25%)		17 (42%)
More than 1 year previously		38 (75%)		23 (58%)
Duration of continuous abstinence during last cessation attempt*	51		39	
< 1 day		5 (10%)		6 (15%)
1–30 days		29 (57%)		14 (36%)
1–5 months		5 (10%)		10 (26%)
≥ 6 months		12 (24%)		9 (23%)
Anyone at Mayo encouraged subject to not smoke after surgery	57	23 (40%)	50	24 (48%)
Stage of change	58		52	
Precontemplation		2 (3%)		0 (0%)
Contemplation		3 (5%)		1 (2%)
Preparation		6 (10%)		5 (10%)
Action		47 (81%)		46 (88%)

Treatment groups were compared using a chi-square test for categorical variables and a rank sum test for continuous variables. Subjects did not differ by randomization group for any characteristic.

* Data are presented for those who indicated at least one previous cessation attempt.

FTND = Fagerström Test for Nicotine Dependence; n = number of observations.

Nine subjects (5 in the placebo group and 4 in the active group) experienced serious adverse events postoperatively, most related to surgical complications (*e.g.*, bowel perforation, hematoma). None were judged likely related to patch therapy. No subject experienced a wound-related complication such as dehiscence or infection.

Subjects receiving the active patch maintained patch usage for a significantly longer period of time postoper-

Table 4. Perceived Stress Scores, Numeric Stress Scores, and Nicotine Withdrawal Scores

	PSS				NSS				NWS			
	Placebo (n = 60)		Active (n = 56)		Placebo (n = 60)		Active (n = 56)		Placebo (n = 60)		Active (n = 56)	
Assessment	n	Median (IQR)	n	Median (IQR)	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Initial (POE)	60	15 (9–21.5)	55	12 (9–19)	60	5.3 ± 2.6	55	4.5 ± 2.6	60	1.7 ± 0.8	55	1.7 ± 0.8
PRE	58	8 (4–13)	56	7 (2.5–14)	59	4.5 ± 2.6	56	3.9 ± 3.1	59	1.1 ± 0.7	56	1.1 ± 0.8
POST	15	6 (4–13)	15	7 (4–9)	23	3.8 ± 3.5	16	3.6 ± 2.9	18	0.7 ± 0.7	15	1.2 ± 0.9
POD2	49	8 (3–15)	46	5.5 (2–11)	50	3.0 ± 2.4	47	2.9 ± 2.6	50	1.1 ± 0.8	47	0.9 ± 0.8
POD3	52	8 (4–12)	48	6 (2.5–12)	52	3.2 ± 2.6	48	2.7 ± 2.4	52	1.1 ± 0.8	48	0.9 ± 0.7
POD8	55	9 (4–15)	49	6 (3–10)	55	3.1 ± 2.4	51	2.6 ± 2.4	55	1.0 ± 0.7	51	0.9 ± 0.7
POD30	49	10 (6–17)	49	10 (6–14)	49	3.5 ± 2.5	49	3.6 ± 2.6	49	1.2 ± 0.7	49	1.2 ± 0.8

The Perceived Stress Score (PSS) was compared between groups at each time point using the rank sum test, and the Numeric Stress Score (NSS) and Nicotine Withdrawal Score (NWS) were compared between groups at each time point using the two-sample *t* test. In all cases, no significant differences between groups were detected. In addition, repeated-measures analyses were performed using data collected from the preoperative assessment through postoperative day (POD) 8. For PSS, the repeated-measures analysis was performed using a square-root transformation. For all variables, the repeated-measures analysis found no significant main effect of treatment ($P = 0.24$, $P = 0.24$, and $P = 0.71$ for PSS, NSS and NWS, respectively) and no evidence of a time-by-treatment interaction ($P = 0.31$, $P = 0.98$, and $P = 0.19$). For NSS, there was evidence of a decline over time ($P = 0.002$); for PSS and NWS, no significant time effect was detected ($P = 0.90$ and $P = 0.87$, respectively).

IQR = interquartile range; n = number of observations; POE = Preoperative Evaluation Center; POST = postoperatively on the day of surgery; PRE = morning of surgery.

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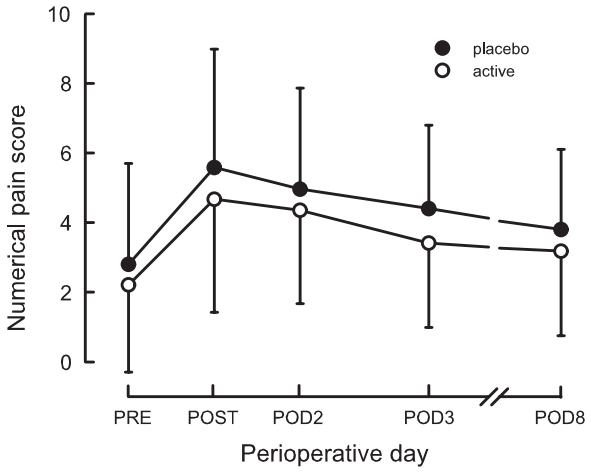

Fig. 2. Numerical Pain Scores over the immediate perioperative period according to study group. Data are presented as mean ± SD. The numbers of subjects with data available at each time period are 59, 32, 54, 53, and 55 for the placebo group and 56, 27, 49, 48, and 50 for the active group. The mean Numerical Pain Score did not differ significantly between groups at any time period. From repeated-measures analysis, the Numerical Pain Score was found to change significantly with time ($P < 0.001$), with no significant main effect of treatment ($P = 0.074$) and no evidence of a time-by-treatment interaction ($P = 0.947$). POD = postoperative day; POST = postoperative on the day of surgery; PRE = morning of surgery.

atively ($P = 0.02$; fig. 4). Subjects receiving the active patch were more likely to definitely recommend patch usage to other smokers undergoing surgery (49% and 71% of subjects in the placebo and active groups, respectively; $P = 0.04$). However, the ability of subjects to correctly identify their group assignment was not significantly different (41% and 55% of subjects in the placebo and active groups, respectively; $P = 0.23$).

In the 5 months after the discontinuation of study patches, 3 subjects sought counseling or enrolled in a program for tobacco dependence (2 placebo, 1 active). Subjects who had received the active patch were significantly more likely to have used additional pharmacotherapy since discontinuing study patches (7% and 23% of subjects in the placebo and active groups, respectively; $P = 0.04$).

Discussion

In cigarette smokers undergoing elective surgery, perioperative NRT does not affect perceived stress or nicotine withdrawal symptoms, and NRT modifies some aspects of smoking behavior in the first 30 days after discharge from the hospital.

Nicotine Replacement Therapy

Nicotine replacement therapy is an important component of tobacco interventions that can approximately double the rate of successful quitting in outpatient settings.[1] However, NRT is seldom used by hospitalized patients.[21] Published experience with NRT specifically in surgical patients is limited. Simon *et al.*[22] evaluated a multicomponent intervention to promote smoking cessation in men after inpatient noncardiac surgery, showing efficacy at 12 months' follow-up (increase in abstinence rates from 8% to 15%). One intervention component included optional NRT (primarily gum), which 65% of subjects used at some time. Ratner *et al.*[23] also implemented an intervention to promote smoking cessation after inpatient noncardiac surgery but did not find efficacy at 12 months postoperatively. NRT (gum) was made available as part of the intervention; no information regarding its use was reported. There is no published experience with NRT in outpatient surgery.

Subjects were recruited based on the intent to use NRT as a tool to manage stress and nicotine withdrawal,

Table 5. Postoperative Cigarette Use

Characteristic	Placebo (n = 60)		Active (n = 56)		*P* Value*
	n	Number (%)	n	Number (%)	
30 days after surgery					
Point prevalence abstinence	60	18 (30%)	56	22 (39%)	0.29
Continuous abstinence	60	15 (25%)	56	16 (29%)	0.66
Change in cigarettes per day from baseline, mean ± SD					
All subjects	60	−11.4 ± 10.9	56	−15.2 ± 10.7	0.045
Those smoking at POD30	42	−6.1 ± 7.0	34	−9.7 ± 7.8	0.027
6 months after surgery					
Point prevalence abstinence	60	11 (18%)	56	10 (18%)	0.95
Continuous abstinence	60	9 (15%)	56	5 (9%)	0.32
Change in cigarettes per day from baseline, mean ± SD					
All subjects	60	−8.4 ± 10.2	56	−8.8 ± 10.5	0.62
Those smoking at 6 months	49	−5.0 ± 7.4	46	−5.3 ± 6.9	0.44

Subjects who were unable to be contacted were assumed to be smoking at the same rate reported at baseline.

* *P* values for categorical variables come from a chi-square test, and *P* values for continuous variables come from a rank sum test.

n = number of observations; POD = postoperative day.

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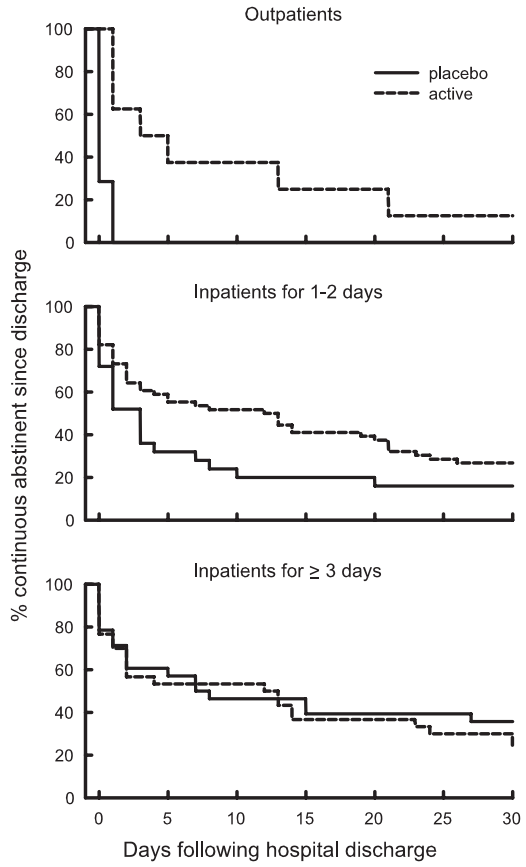

Fig. 3. Percentages of subjects continuously abstinent after discharge from the hospital according to study group: outpatients (n = 15; 7 placebo, 8 active); inpatients hospitalized for 1 or 2 days (n = 43; 25 placebo, 18 active); and inpatients hospitalized for 3 or more days (n = 58; 28 placebo, 30 active). For subjects who reported smoking, the date of relapse was obtained by self-report at each contact. Subjects who discontinued study participation and were not already known to have relapsed to smoking (n = 11; 6 placebo, 5 active) were assumed to have resumed smoking the day after their last study contact. From proportional hazards regression analyses, a significant interaction ($P = 0.05$) was detected between hospital length of stay (LOS) and treatment assignment. Curves were subsequently calculated separately for each LOS group using the Kaplan-Meier method and compared between groups using the log rank test ($P = 0.002$ for outpatients, $P = 0.078$ for those with LOS of 1 or 2 days, $P = 0.693$ for those with LOS of 3 or more days).

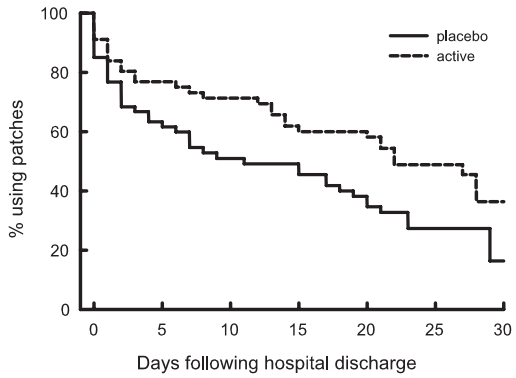

Fig. 4. Percentages of subjects using study patches after discharge from the hospital according to study group. Date of last patch use was obtained *via* self-report at the 30-day follow-up contact. Subjects who discontinued study participation before day 30 and who had not already indicated discontinuing study medication (n = 9; 5 placebo, 4 active) were assumed to have discontinued use of study patches on the day after their last study contact. Subjects who did not discontinue study participation but had missing information regarding the date of last patch use (n = 4; 2 placebo, 2 active) were censored at the date they were last known to be using study patches. Curves were calculated using the Kaplan-Meier method and compared between groups using the log rank test ($P = 0.018$).

rather than as an aid to achieve long-term cessation. In a previous observational study of smoking behavior in a general surgical population also recruited through our Preoperative Evaluation Center, 37% were in the action stage preoperatively (*i.e.*, planned to maintain postoperative abstinence),[13] compared with 85% of subjects in the current study. Therefore, although subjects were advised that the purpose of NRT in this study was to manage nicotine withdrawal, we recruited a population of smokers who were motivated to quit. Subjects were also highly dependent on nicotine; 48% reported a Fagerström Test for Nicotine Dependence score of greater than 6, whereas 28% had scores in this range in our previous observational study.[13] Therefore, like many studies of interventions to change smoking behavior, the subjects in this study are not representative of the general population of smokers scheduled to undergo elective surgery, but rather those more motivated to modify their smoking behavior.

Stress and Nicotine Withdrawal

The relation between cigarette smoking and stress is complex. Paradoxically, although smoking a cigarette generally acutely reduces measures of stress, smokers (including those scheduled to undergo elective surgery) report increased baseline levels of stress compared with nonsmokers, and perceived stress eventually decreases after smokers quit.[4,5] The measures of stress used in the current study were the same as used in our previous observational study, which compared perioperative changes in stress in smokers and nonsmokers undergoing elective surgery.[13] The values obtained in the current study are similar to those observed in smokers in the previous study. We also confirm our previous observation that PSS and NSS values decreased from the initial evaluation in the Preoperative Evaluation Center (at least 1 day before surgery) to the preoperative evaluation (the morning of surgery). In our previous work, we speculated that the anticipation of imminent beneficial surgery or the presence of social support provided by family members in the immediate preoperative period may explain this finding; the current results do not provide basis for further speculation.

The finding that treatment group assignment had no effect on the PSS or the NSS does not support the hypothesis that NRT decreases psychological stress in cigarette smokers scheduled to undergo elective surgery. This may reflect the fact that NWS values were

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relatively low in both groups and were also not affected by treatment assignment. That is, even subjects receiving placebo patches had few complaints of nicotine withdrawal symptoms. This could represent a placebo effect of the patches. However, the NWS values in the current study were very similar to those noted in our previous observational study, in which no intervention was provided.[13] In that study, we also could find little evidence of significant exacerbations in nicotine withdrawal symptoms in the perioperative period, even when the specific craving item of the NWS was analyzed in highly dependent smokers. Therefore, these studies support the concept that nicotine withdrawal symptoms do not consistently contribute to distress in surgical patients. Some previous studies also suggest that other stressful situations demanding forced abstinence, such as military training, may also lessen the impact of nicotine withdrawal symptoms.[24,25] It is also possible that anesthetic drugs or adjuvants (especially analgesics) could affect nicotine withdrawal symptoms. For example, opioid receptors may modulate nicotine withdrawal in animals.[26,27]

Pain was measured to determine whether differences in pain perception might contribute to hypothesized differences in stress. In our previous work, we found that although smokers undergoing elective surgery reported higher overall pain scores than nonsmokers, the changes in scores over the perioperative period were similar.[13] In the current study, postoperative pain scores were not different between groups. However, because surgical procedures (and thus the magnitude of the painful stimulus) were not exactly matched between groups and because perioperative analgesia was not standardized, our study design does not permit conclusions regarding the possible impact of NRT on postoperative pain. Nicotine can have analgesic effects in humans and has recently proved beneficial in relieving postoperative pain in nonsmokers.[28] Whether this action also occurs in smokers, who experience chronic changes in nicotinic receptor pharmacology, with nicotine in doses provided by NRT remains to be determined.[29,30]

Smoking Behavior

To properly interpret the data regarding smoking behavior, three factors must be considered. First, the stated purpose of the study was not to promote sustained abstinence; although subjects were told that it would be desirable to prolong postoperative patch use and abstinence as long as possible, no other smoking-cessation interventions were provided. However, as noted above, many subjects were clearly motivated to quit and undoubtedly viewed study patches as a tool to help them do so. Second, with the exception of the immediate preoperative assessment, we used patient self-report to ascertain smoking behavior because many of the subjects could not return for follow-up. Self-report has been shown to be relatively reliable,[31] but it is possible that actual abstinence rates were lower than reported. As is customary, subjects who were not able to be contacted were assumed to be smoking. Finally, even small differences in postoperative abstinence rates can be clinically significant, given the considerable benefits of abstinence to health. The number of subjects studied was chosen based on the ability to evaluate the primary endpoint of perceived stress, and the power to detect relatively small differences in postoperative abstinence rates was not high.

Although most subjects expressed a desire preoperatively to maintain postoperative abstinence, most did not do so, with 34% self-reporting abstinence at 30 days after discharge from the hospital. This proportion is higher than that of subjects in our previous observational study (18%),[13] which may reflect the fact that a higher proportion of subjects were in the action stage in the current study. Overall abstinence rates were not significantly affected by treatment assignment, although there was a tendency for higher abstinence rates at POD30 in subjects receiving active patch. However, even in the absence of any other intervention, NRT changed some aspects of postoperative smoking behavior. Subjects with short hospital stays who received active patches tended to delay resumption of smoking. The reason why this treatment effect depended on hospital LOS is unclear, but is encouraging because the majority of surgical patients in the United States now undergo outpatient or short-stay surgery. We speculate that NRT may have had a greater effect on behavior in short-stay settings because these patients were otherwise free to resume smoking at home, unlike in the inpatient setting, in which abstinence was mandated while in the hospital, regardless of treatment assignment. Overall, patients receiving active patch reduced their cigarette consumption (compared with preoperative levels) more than subjects receiving placebo patches. This effect is consistent with previous studies showing that patients who still smoke while receiving nicotine patches reduce their cigarette consumption to maintain relatively constant plasma nicotine concentrations.[32,33] To the extent that nonnicotine components of cigarette smoke, such as carbon monoxide, contribute to postoperative complications, this reduction in consumption may be beneficial, although this speculation requires confirmation.

Treatment assignment also affected subjects' use of the study patches. Although subjects were unable to correctly identify group assignment, those receiving active patches used them for a longer period of time postoperatively and were more likely to recommend patch use. The finding that subjects receiving active patch were also more likely to use pharmacotherapy after POD30 further suggests that subjects perceived a benefit of NRT.

Surgeons may be reluctant to use NRT in their patients because of concerns regarding the possible adverse effects of nicotine on bone and wound healing.[6–8] Al-

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though active smokers are at risk for these complications, the role of nicotine in the doses provided by NRT is unclear in comparison with the effects of other components of cigarette smoke or the vascular disease caused by smoking. Recent evidence in human subjects suggests that smoking cessation with the aid of NRT significantly reduces the rates of wound-related complications.[34] No wound-related complications were observed in the current study, although the power of the study to detect these relatively rare events was not high (upper limit of 95% confidence interval for no events of 6%). We also found no evidence for adverse effects related to patch therapy, because the frequency of adverse events was not different between groups. Therefore, although larger studies are required, this report provides preliminary evidence that NRT is safe and well tolerated in the surgical population.

In conclusion, routine NRT is not indicated in smokers undergoing elective surgery for the purposes of managing nicotine withdrawal and stress. However, NRT does modify some aspects of postoperative smoking behavior, especially in patients with shorter hospital stays. Given that NRT was well tolerated in these subjects, future studies should explore its role as a component of interventions to maintain prolonged postoperative abstinence from smoking.

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