

# Individualizing Nicotine Replacement Therapy for the Treatment of Tobacco Dependence

## A Randomized Trial

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**Background:** Despite the well-documented efficacy and different pharmacokinetic and pharmacodynamic properties of different forms of nicotine replacement therapy, empirical data are insufficient to guide practitioners in selecting a particular form of treatment for individual patients with tobacco dependence.

**Objective:** To evaluate the comparative efficacy of transdermal nicotine and nicotine nasal spray and identify predictors of treatment outcome.

**Design:** Randomized, open-label clinical trial with a 6-month follow-up period.

**Setting:** 2 university-based smoking cessation research programs.

**Participants:** 299 treatment-seeking smokers who were followed for 6 months after the target quit date.

**Intervention:** Behavioral group counseling and 8 weeks of therapy with nicotine nasal spray or transdermal nicotine.

**Measurements:** Demographic characteristics, smoking history,

depression symptoms, and body mass index were measured at baseline. Smoking practices were biochemically verified at the end of treatment and at 6 months after the target quit date.

**Results:** Abstinence rates for the transdermal nicotine and nicotine nasal spray groups were not significantly different at 6-month follow-up (15.0% vs. 12.2%, respectively;  $P > 0.2$ ). Interactions in abstinence rates for subgroups of smokers were statistically significant ( $P < 0.05$ ). Smokers who had low to moderate dependence levels, were not obese, and were white achieved higher abstinence rates with transdermal nicotine, whereas smokers who were highly dependent, obese, or members of minority groups achieved higher abstinence rates with nasal spray.

**Limitations:** The subgroup findings need confirmation in additional large studies before they are routinely applied.

**Conclusions:** Ethnicity, weight, and level of nicotine dependence may help identify smokers who have greater or lesser abstinence rates with either transdermal or nasal spray nicotine.

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Nicotine replacement therapy is recommended as a first-line treatment for tobacco dependence (1). Although use of nicotine replacement therapy can double a person's odds of quitting smoking, as many as 70% to 80% of smokers receiving treatment do not achieve long-term abstinence (2–5). Nicotine replacement therapy is widely used; however, empirical data are insufficient to guide practitioners in selecting a particular form of treatment for individual patients with tobacco dependence (1). In lieu of such evidence, the most rational approach has been to base the choice of pharmacotherapy on the patient's previous treatment experiences and preferences (6). However, recent data suggest that smokers' past experiences and preferences have little bearing on the outcome of nicotine replacement therapy (7).

Our goal was to evaluate the comparative efficacy of transdermal nicotine and nicotine nasal spray and to identify pretreatment clinical characteristics that predict treatment outcome. In addition, to suggest factors that may be useful for individualizing nicotine replacement therapy, we examined predictors of treatment outcome by using subgroup analyses. These 2 forms of nicotine replacement therapy were selected on the basis of their differing pharmacokinetic and pharmacodynamic properties. After administration of transdermal nicotine, levels of nicotine rise slowly and then plateau within 4 to 6 hours (8). This profile is believed to be optimal for alleviating withdrawal

symptoms and perhaps reducing positive reinforcement from nicotine when subsequent exposure to tobacco occurs (that is, a brief lapse or "slip") (9, 10). In contrast, nicotine nasal spray produces rapid peak venous levels of nicotine, which lead to rewarding effects that more closely approximate those achieved from cigarette smoking (9, 11, 12).

## METHODS

Participants were enrolled at Georgetown University (Washington, DC) and the University of Pennsylvania (Philadelphia, Pennsylvania). The institutional review boards from both universities approved the research procedures. Figure 1 shows the flow of participants through the enrollment, treatment, and follow-up phases of the trial.

Smokers responding to local media advertisements for free smoking cessation treatment and to physician referrals were screened for eligibility and recruited from February 2000 through March 2002. Eligible persons were current cigarette smokers 18 years of age or older who had smoked 10 or more cigarettes per day for the previous 12 months. Exclusion criteria were pregnancy or lactation, uncontrolled hypertension, unstable angina, heart attack or stroke within the previous 6 months, current treatment or recent diagnosis of cancer, drug or alcohol dependence, current diagnosis or history of a psychotic disorder, or cur-

rent use of bupropion or nicotine-containing products other than cigarettes.

### Study Design and Treatment Procedures

This was a randomized, open-label clinical trial of transdermal nicotine versus nicotine nasal spray for smoking cessation. Randomization was determined by using a computer-generated randomization scheme operated by a senior data manager; stratification was done by study site. Allocation to treatment could not be concealed from the counselors or the study assistants who delivered the medication to patients after preparation at the research pharmacy.

All participants received 7 sessions of standardized behavioral group counseling that included instruction in the management of smoking triggers, relapse prevention, and stress management techniques. The behavioral counseling sessions, which occurred in the evening, lasted approximately 1.5 hours each and included approximately 10 to 14 members per group. As reported previously (13), 70% of participants completed all 7 sessions, and differences in completion rates by study site were not statistically significant. At each site, two counselors with master's degrees led an equal number of groups receiving either transdermal nicotine or nicotine nasal spray therapy and received weekly supervision to ensure protocol adherence.

Nicotine nasal spray therapy (Nicotrol, Pharmacia and Upjohn, Helsingborg, Sweden) was initiated on the target quit date (week 3) and was delivered over an 8-week period. At the second counseling session (week 2), participants were shown how to deliver a 1.0-mg dose (0.5-mg spray in each nostril) and how to use nicotine nasal spray 8 to 40 times per day (with a maximum of 5 doses/h) beginning on the target quit date. After 4 weeks of use, participants were instructed to taper their nicotine nasal spray dose by one third for a 2-week period and then by another third for the final 2 weeks of treatment.

Participants used transdermal nicotine (Nicoderm CQ, GlaxoSmithKline, Research Triangle Park, North Carolina) over an 8-week treatment period, beginning with the morning of the target quit date (week 3). A 24-hour, tapered-dose formulation was used: 4 weeks at 21 mg, 2 weeks at 14 mg, and 2 weeks at 7 mg.

To assess smoking status, we conducted telephone interviews at the end of treatment (8 weeks after the target quit date) and 6 months after the target quit date; a standard timeline follow-back method was used (14). Interviewers were blinded to study group assignment. Participants who reported complete abstinence (not even a puff of a cigarette) for at least 7 days before the assessment were asked to complete an in-person visit for biochemical verification of abstinence within 1 to 2 weeks after the follow-up interview.

Adverse events were self-reported by using a weekly checklist that queried the severity of 17 common side effects associated with nicotine replacement therapy (for ex-

### Context

Do certain forms of nicotine replacement therapy work better than others and, if so, in whom?

### Contribution

This randomized trial of 299 treatment-seeking smokers found similar 6-month abstinence rates between smokers receiving behavioral counseling and 8 weeks of therapy with either nicotine nasal spray (12%) or transdermal nicotine (15%). Subgroup analyses suggested that highly dependent, obese, and nonwhite smokers achieved higher abstinence rates with nasal spray. Low to moderately dependent, nonobese, and white smokers achieved higher abstinence rates with transdermal nicotine.

### Cautions

Tailoring nicotine replacement therapy on the basis of characteristics of smokers is an intriguing strategy but has not yet been tested.

—The Editors

ample, rash with transdermal nicotine). Research assistants evaluated the completed checklist before each counseling visit and reviewed it with the study physicians and participants, as needed.

### Measurements

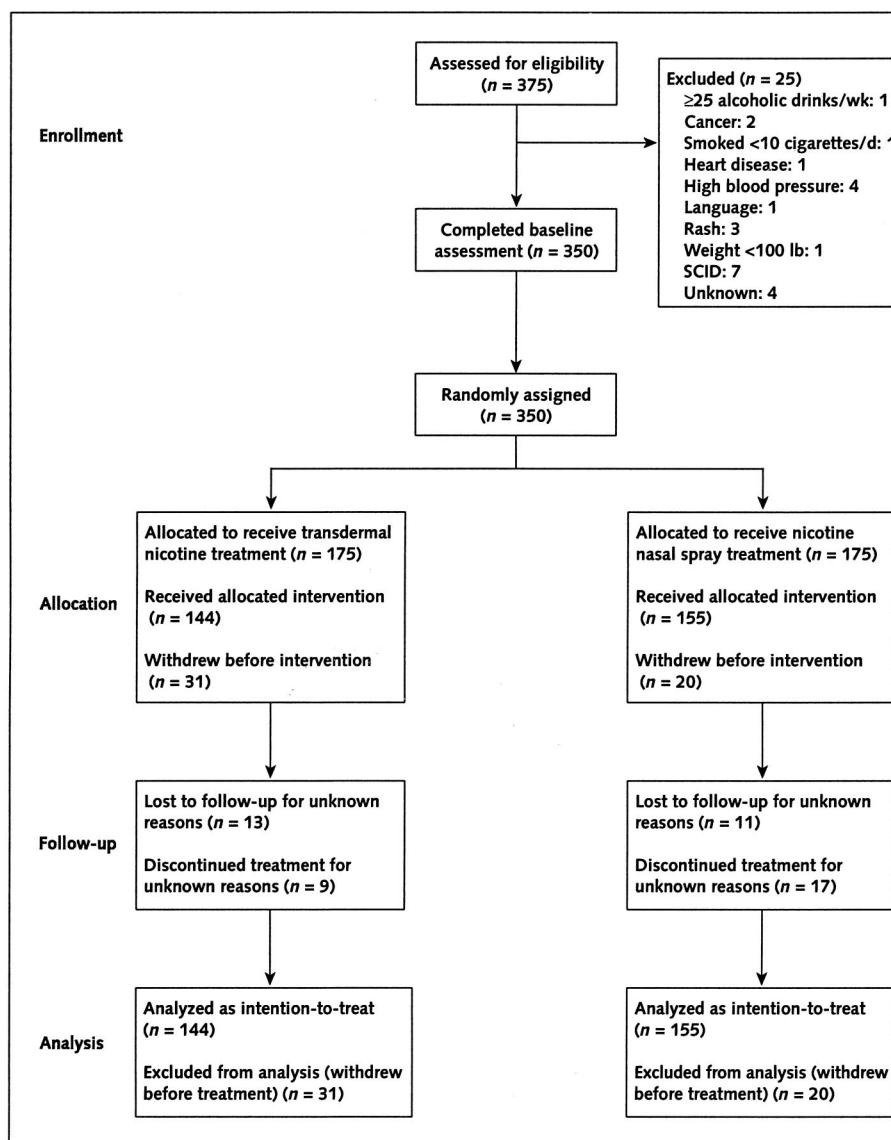
#### Predictors

On the basis of previous research and ease of assessment, we selected the following variables as predictors: sex, ethnicity, education, body mass index (BMI), nicotine dependence, and depression symptoms (15–18). We used the Fagerstrom Test for Nicotine Dependence (19) to measure tobacco dependence; a cutoff score of 7 or greater was used to classify participants as highly nicotine dependent (20). The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess the severity of depression symptoms; a score 16 or greater was used to identify clinical symptoms of depression (21). Height and weight were measured at the medical screening visit. Body mass index was calculated by dividing weight in kilograms by height in millimeters (squared), and obesity was defined according to recommendations of the National Institutes of Health ( $BMI \geq 30 \text{ kg/m}^2$ ) (22).

#### Treatment Monitoring

Participants recorded their daily use of nicotine replacement therapy. Those assigned to transdermal nicotine recorded their daily application of patches, and those assigned to nicotine nasal spray recorded the number of doses per day. Because use of nicotine replacement therapy may be confounded with smoking status (that is, participants may discontinue nicotine replacement therapy if they have relapses), we focused on average use during the first 2 weeks of treatment.

Figure 1. Flow diagram of trial participation.



SCID = severe combined immunodeficiency disease.

We calculated the percentage of cotinine replacement from treatment by dividing participants' plasma cotinine levels after 1 week of treatment by their pretreatment plasma cotinine levels (23). These time points were selected to coincide with a period of regular smoking and with steady-state cotinine levels achieved after treatment (23). Cotinine levels were analyzed by using gas chromatography with nitrogen phosphorus detection, modified for analysis by using a capillary gas chromatography column (24).

### Outcomes

We used prolonged abstinence as the primary outcome measure and point prevalence as the secondary measure (25). For prolonged abstinence, relapse was defined as 7 consecutive days of smoking at any time during the

follow-up period. Because the prolonged abstinence measurement period extends from the target quit date to 6-month follow-up, biochemical verification for this period, by definition, is not possible. The point prevalence measure required 7 days of continuous abstinence immediately before the follow-up point, which was confirmed by a carbon monoxide reading of less than 10 parts per million (ppm) (26). (Of note, of the 65 participants who self-reported 7 days of abstinence and provided a carbon monoxide sample, 15 [23%] had a carbon monoxide level  $\geq 10$  ppm). Thus, for prolonged abstinence, brief relapses or slips (that is, any smoking at all, even a puff) were allowed, whereas the point prevalence measure allowed no lapses during the 7 days before each follow-up (25). For descriptive purposes, we also assessed rates of continuous absti-

**Table 1. Baseline Characteristics of Sample by Treatment Group**

Characteristic	Transdermal Nicotine Group (n = 144)	Nasal Spray Group (n = 155)
Men	73 (51)	64 (41)
Ethnicity		
White	89 (62)	102 (66)
Other	55 (38)	53 (34)
Education		
Some college	71 (49)	69 (45)
Graduated college	73 (51)	86 (56)
Nicotine dependence*		
Low to moderate	103 (72)	99 (64)
High	41 (29)	56 (36)
Body mass index		
Nonobese	104 (72)	115 (74)
Obese	40 (28)	40 (26)
Depression symptoms		
Absent	110 (76)	114 (74)
Present	34 (24)	41 (27)
Enrollment site		
Georgetown University	104 (72)	101 (65)
University of Pennsylvania	40 (28)	54 (35)

\* High nicotine dependence refers to a score of 7 or greater on the Fagerstrom Test for Nicotine Dependence (19).

nence under the most stringent criterion (not even a puff) from target quit date to 6-month follow-up (not biochemically verified). In intention-to-treat analyses, we presumed that those who dropped out or were otherwise lost to follow-up had had relapses.

### Statistical Analysis

We calculated that a sample size of at least 140 people per group was necessary to detect a between-group difference in quit rates of 8% or greater with a power of 80% ( $\alpha = 0.05$ ) (PASS, NCSS, Kaysville, Utah).

We used chi-square and Wilcoxon rank-sum tests to examine pretreatment variables by treatment group assignment and to compare treatment groups on the abstinence outcomes. Logistic regression analysis was used to examine the independent effects of treatment group assignment, pretreatment variables, and their interactions on prolonged abstinence and verified point prevalence abstinence. We used Wilcoxon rank-sum tests to examine differences be-

tween treatment groups in use and percentage of cotinine replacement.

### Role of the Funding Sources

The funding sources had no role in the design or conduct of this analysis or in the decision to submit the paper for publication.

## RESULTS

**Table 1** shows characteristics of participants by treatment group. Fifty-four percent of participants were women, 53% were college graduates, and the mean ( $\pm$ SD) age of participants was  $46 \pm 11$  years. Sixty-four percent of participants were white, 27% were African American, 3% were Hispanic, 2% were Asian, and 4% reported other ethnicities. On average, participants smoked a mean ( $\pm$ SD) of  $21 \pm 11$  cigarettes per day and had mean ( $\pm$ SD) baseline cotinine levels of  $217.1 \pm 137.1$  nmol/L. Fifty percent of smokers had previous experience with transdermal nicotine, whereas only 2% had used nicotine nasal spray.

Although the proportion of participants assigned to each treatment group did not differ by study site, participants enrolled at the University of Pennsylvania were significantly more likely to be nonwhite ( $P = 0.04$ ), to be obese ( $P = 0.002$ ), and to have lower levels of education ( $P = 0.003$ ). We controlled for these variables in the logistic regression models of abstinence.

Site differences were not significant among participants in sex, age, and nicotine dependence level. Ninety-two percent of participants completed the 6-month follow-up assessment; participants who remained in the study did not differ from those who were lost to follow-up in terms of group assignment or baseline characteristics ( $P > 0.10$  for all comparisons).

### Treatment Outcome

None of the participants reported any serious adverse events. As shown in **Table 2**, 62.5% of the transdermal nicotine group achieved prolonged abstinence through the end of treatment compared with 44.5% of the nicotine nasal spray group ( $P = 0.002$ ). At 6-month follow-up, differences in prolonged abstinence rates were not statistically

**Table 2. Abstinence Rates by Group and Outcome**

Outcome	End of Treatment				6-Month Follow-up			
	Transdermal Nicotine Therapy	Nasal Spray Therapy	Difference (95% CI)	P Value	Transdermal Nicotine Therapy	Nasal Spray Therapy	Difference (95% CI)	P Value
	%	%	percentage points		%	%	percentage points	
Prolonged abstinence*	62.5	44.5	18 (6.88 to 29.12)	0.002	28.5	24.5	4 (-6.01 to 14.01)	>0.2
Continuous abstinence	25.7	21.3	4.4 (-5.22 to 14.02)	>0.2	15.0	12.2	2.8 (-4.98 to 10.58)	>0.2
Point prevalence†	34.7	29.0	5.7 (-4.86 to 16.26)	>0.2	18.1	15.5	2.6 (-5.59 to 11.08)	>0.2

\* Seven days of consecutive smoking at any time during the follow-up period is defined as a treatment failure, and therefore, periodic brief lapses, or "slips," are allowed. This outcome is not biochemically verified.

† Seven days of consecutive abstinence before the follow-up point is required. No slips are allowed, and this outcome is biochemically verified (47).

Table 3. Logistic Regression Models of Abstinence at the 6-Month Follow-up

Variable	Prolonged Abstinence		Point Prevalence	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Sex				
Male = 0				
Female = 1	0.43 (0.25–0.76)	0.003	0.91 (0.48–1.72)	>0.2
Education				
Some college = 0				
Graduated college = 1	1.24 (0.70–2.18)	>0.2	1.28 (0.66–2.46)	>0.2
Ethnicity				
Other = 0				
White = 1	1.20 (0.52–2.74)	>0.2	2.41 (0.86–6.77)	>0.2
Depression				
Absent = 0				
Present = 1	0.75 (0.39–1.44)	>0.2	0.76 (0.36–1.61)	>0.2
Nicotine dependence				
Low to moderate = 0				
High = 1	0.30 (0.12–0.82)	0.02	0.48 (0.16–1.43)	0.19
Obesity				
Nonobese = 0				
Obese = 1	0.39 (0.15–1.01)	0.05	0.44 (0.14–1.39)	0.16
Treatment				
Transdermal nicotine therapy = 0				
Nasal spray therapy = 1	0.92 (0.34–2.48)	>0.2	1.07 (0.31–3.76)	>0.2
Treatment × ethnicity	0.30 (0.09–0.94)	0.04	0.20 (0.05–0.77)	0.02
Treatment × obesity	3.92 (1.20–14.01)	0.03	3.77 (0.83–17.0)	0.08
Treatment × dependence	3.73 (1.05–13.29)	0.04	4.10 (1.00–16.81)	0.05

significant (28.5% vs. 24.5%; difference, 4 percentage points [CI, –6.01 to 14.01 percentage points]). Point prevalence and continuous abstinence rates did not differ by treatment group assignment.

Table 3 shows the logistic regression models. The relative efficacy of transdermal nicotine and nicotine nasal spray in producing prolonged abstinence was altered by participants' pretreatment characteristics, as indicated by 3 statistically significant interaction effects: treatment × ethnicity, treatment × BMI, and treatment × nicotine dependence. Transdermal nicotine was superior to nicotine nasal spray for white smokers, nonobese smokers, and smokers with low to moderate levels of nicotine dependence. The reverse was true for smokers in minority groups, obese smokers, and smokers with high levels of nicotine dependence. The results were similar for the point prevalence outcome, although the treatment by BMI interaction did not achieve statistical significance ( $P = 0.08$ ) (Figure 2).

#### Use and Percentage of Cotinine Replacement

During the first 2 weeks of treatment, the mean ( $\pm$ SD) number of daily doses of nicotine nasal spray was  $7.5 \pm 6.9$  (range, 0 to 32), and the mean ( $\pm$ SD) number of days per week of transdermal nicotine use was  $6.4 \pm 1.1$ . Mean percentage ( $\pm$ SD) of cotinine replacement among participants with carbon monoxide-verified abstinence ( $<10$  ppm) at session 4 was  $139\% \pm 152\%$  for the transdermal nicotine group and  $66\% \pm 103\%$  for the nicotine nasal spray group ( $P < 0.001$ ).

We conducted post hoc exploratory analyses of nicot-

tine replacement therapy use and percentage of cotinine replacement to explain the different treatment responses. Obese smokers used nicotine nasal spray more frequently than did nonobese smokers (9.8 vs. 6.8 sprays) ( $P = 0.03$ ). The patterns were reversed for transdermal nicotine (6.0 vs. 6.6 d/wk for obese and nonobese smokers, respectively) ( $P = 0.01$ ). Percentage replacement did not differ statistically for obese compared with nonobese smokers overall or in each treatment group ( $P > 0.10$  for all comparisons). Highly dependent smokers reported more frequent use of nicotine nasal spray than did less dependent smokers (9.2 vs. 6.3 sprays) ( $P = 0.01$ ), and the patterns were reversed for transdermal nicotine users (6.1 vs. 6.5 d/wk) ( $P = 0.06$ ). Highly dependent smokers in the transdermal nicotine group had lower percentage replacement than did less dependent smokers (89% vs. 150%) ( $P = 0.001$ ), but there was no statistically significant difference in percentage replacement by dependence level in the nicotine nasal spray group ( $P > 0.2$ ). Ethnicity was unrelated to transdermal nicotine and nicotine nasal spray use or percentage replacement.

The level of use of transdermal nicotine was correlated with percentage replacement ( $P = 0.04$ ) but was unrelated to 6-month prolonged abstinence rates ( $P = 0.15$ ). By contrast, use of nicotine nasal spray was unrelated to percentage replacement ( $P > 0.2$ ) but was a statistically significant predictor of 6-month prolonged abstinence ( $P = 0.04$ ). Percentage of cotinine replacement was not related to 6-month abstinence rates in the total sample or in either treatment group ( $P \geq 0.10$  for all comparisons).

## DISCUSSION

We believe that this is the first clinical trial to suggest factors for individualizing nicotine replacement therapy on the basis of pretreatment characteristics. Six-month abstinence rates for the transdermal nicotine and nicotine nasal spray groups were not statistically significantly different overall, and abstinence rates were similar to those achieved in previous studies (27–29). However, treatment outcomes for subgroups of smokers were clinically and statistically different. Smokers with low to moderate dependence levels, nonobese smokers, and white smokers achieved higher abstinence rates with transdermal nicotine, whereas highly dependent, obese, and minority group smokers achieved higher abstinence rates with nasal spray. The magnitude of the differences in outcomes among these subgroups of smokers was similar to the differences in abstinence rates achieved when active medication was compared with placebo (27). Although these pretreatment variables were selected on the basis of previous research (15–18), we did not have an a priori hypothesis for factor by treatment interaction effects. Therefore, these results should be considered hypothesis-generating and must be confirmed in future work.

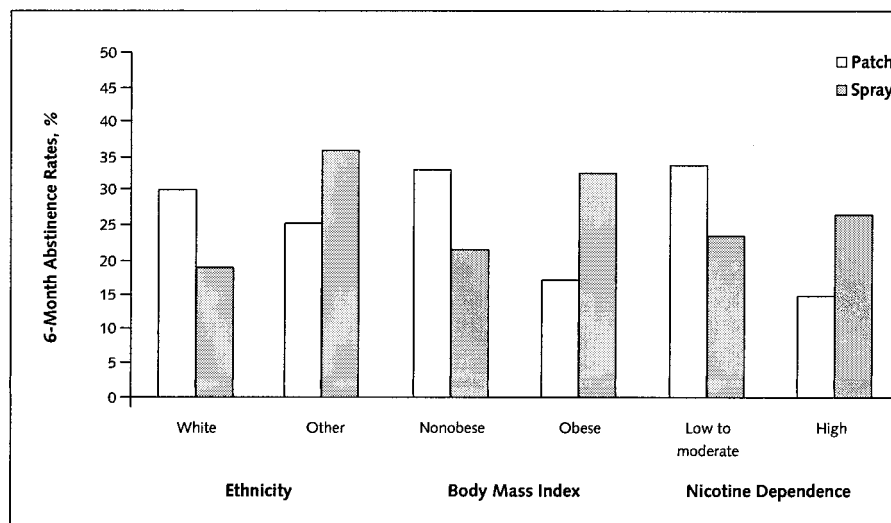
In previous trials of transdermal nicotine, measures of nicotine dependence predicted outcome in some studies (30, 31) but not others (32). Consistent with our findings for the benefits of transdermal nicotine for less dependent smokers, Paoletti and colleagues (30) reported that smokers with lower baseline cotinine levels achieved significantly higher abstinence rates with transdermal nicotine than with placebo. In contrast, a previous trial that compared nicotine nasal spray with placebo documented a greater beneficial effect of the nasal spray for the heaviest smokers (33). These investigations examined predictors of response to a single nicotine replacement therapy compared with

placebo. To our knowledge, our study is the first to demonstrate that the relative efficacy of these alternative forms of nicotine replacement therapy differs depending on smokers' pretreatment levels of nicotine dependence.

Several mechanisms may be responsible for the different responses to these treatments. Consistent with previous research (5, 7), more highly dependent smokers used nicotine nasal spray more frequently than less dependent smokers. However, percentage cotinine replacement after use of nicotine nasal spray did not differ significantly for highly dependent and less dependent smokers. This suggests that smokers self-administered nasal spray to achieve nicotine levels comparable to those achieved from smoking. In addition, use of nicotine nasal spray was positively associated with abstinence, whereas use of transdermal nicotine was not. These results suggest that the ability to self-administer nicotine nasal spray when desired and the reinforcing effects of more rapidly delivered nicotine (9) may be the most important factors in facilitating abstinence for more highly dependent smokers.

The pattern of results for obese smokers was similar to that of highly dependent smokers. Swan and colleagues (16) reported that smokers with a higher BMI were significantly more likely to relapse if they were using transdermal nicotine at a dose of 14 mg (16). The authors suggested that this result may be attributable to lower levels of nicotine replacement in obese compared with nonobese smokers (34), a finding not supported by our study. An alternative explanation for the advantage of the nasal spray in obese smokers is that these smokers may be particularly sensitive to smoking cessation treatments that provide positive reinforcement. Both food and nicotine provide substantial positive reinforcement, which is mediated by stimulation of dopamine activity (35). Evidence also shows that obesity and smoking may share a common genetic basis

Figure 2. Six-month prolonged abstinence rates for treatment group by ethnicity, body mass index, and nicotine dependence.



related to brain reward pathways (36–38). Because obese persons have less access to alternative sources of reinforcement (39), the positive reinforcement derived from nicotine nasal spray may facilitate abstinence to a greater degree than does the relief from withdrawal provided by transdermal nicotine.

Our results also support the premise that members of different ethnic groups may require different forms of treatment for tobacco dependence (40). Compared with white smokers, African-American smokers use fewer cigarettes per day and are more likely to smoke mentholated cigarettes (41, 42). African-American smokers also have higher serum cotinine levels (43) and may extract more nicotine per cigarette than do white smokers (44). Smoking fewer cigarettes per day but taking in more nicotine per cigarette suggests that African-American smokers are smoking to obtain peak nicotine levels and therefore may achieve greater benefits from the nasal spray. Because ethnicity was a predictor of treatment outcome even when adjustments were made for educational level, it is unlikely that the observed ethnic differences are explained by socioeconomic status (45).

Our study has several limitations. First, we used an open-label design. Because the similar efficacies of transdermal nicotine and nicotine nasal spray relative to placebo were established (2, 29, 33, 46, 47), we chose the design to limit participant burden, improve adherence, and closely simulate usual clinical regimens. Second, because transdermal nicotine provided substantially higher levels of nicotine replacement than did nicotine nasal spray, we cannot separate the effects of nicotine delivery method from overall nicotine replacement. However, our results did not provide evidence for an effect of nicotine replacement level on abstinence, which supports the premise that treatment effects in subgroups may be attributable to differences in the speed of nicotine delivery. Third, we cannot rule out other interpretations for the enhanced efficacy of nicotine nasal spray in particular subgroups, including the possibility that more active treatment approaches (for example, nicotine nasal spray) may work better than passive methods (for example, transdermal nicotine) for some smokers. Fourth, we included few participants in ethnic groups other than African American and had limited ability to detect effect differences among ethnic groups. Fifth, delivery of behavioral counseling by particular counselors and unique characteristics of the volunteer participants and study sites may limit generalizability.

Despite its limitations, we believe that our study provides an important step toward helping clinicians and patients individualize the choice of nicotine replacement therapy. Although additional studies are needed to validate the utility of matching treatment to smoker's individual characteristics, our results suggest that transdermal nicotine is an effective treatment for nonobese, white, and low nicotine-dependent smokers. In contrast, nicotine nasal spray

may be more beneficial for obese smokers, highly dependent smokers, and members of minority groups.

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## References

1. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA*. 2000;283:3244-54. [PMID: 10866874]
2. Transdermal nicotine for smoking cessation. Six-month results from two multicenter controlled clinical trials. Transdermal Nicotine Study Group. *JAMA*. 1991;266:3133-8. [PMID: 1956099]
3. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. *JAMA*. 1994;271:1940-7. [PMID: 8201739]
4. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2002;CD000146. [PMID: 12519537]
5. Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Arch Intern Med*. 1999;159:2033-8. [PMID: 10510989]
6. Hughes JR, Goldstein MG, Hurt RD, Shiffman S. Recent advances in the pharmacotherapy of smoking. *JAMA*. 1999;281:72-6. [PMID: 9892454]
7. West R, Hajek P, Nilsson F, Foulds J, May S, Meadows A. Individual differences in preferences for and responses to four nicotine replacement products. *Psychopharmacology (Berl)*. 2001;153:225-30. [PMID: 11205423]
8. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. *J Consult Clin Psychol*. 1993;61:743-50. [PMID: 8245272]
9. Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med*. 1995;333:1196-203. [PMID: 7565976]
10. Hughes JR. Pharmacotherapy for smoking cessation: unvalidated assumptions, anomalies, and suggestions for future research. *J Consult Clin Psychol*.

- 1993;61:751-60. [PMID: 8245273]
11. Johansson CJ, Olsson P, Bende M, Carlsson T, Gunnarsson PO. Absolute bioavailability of nicotine applied to different nasal regions. *Eur J Clin Pharmacol.* 1991;41:585-8. [PMID: 1815971]
  12. Benowitz NL. Pharmacology of nicotine: addiction and therapeutics. *Annu Rev Pharmacol Toxicol.* 1996;36:597-613. [PMID: 8725403]
  13. Patterson F, Jepson C, Kaufmann V, Rukstalis M, Audrain-McGovern J, Kucharski S, et al. Predictors of attendance in a randomized clinical trial of nicotine replacement therapy with behavioral counseling. *Drug Alcohol Depend.* 2003;72:123-31. [PMID: 14636967]
  14. Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, Miller IW. Reliability and validity of a smoking time-line follow-back interview. *Psychol Addict Behav.* 1998;12:101-12.
  15. Gilpin EA, Pierce JP. Demographic differences in patterns in the incidence of smoking cessation: United States 1950-1990. *Ann Epidemiol.* 2002;12:141-50. [PMID: 11897171]
  16. Swan GE, Jack LM, Ward MM. Subgroups of smokers with different success rates after use of transdermal nicotine. *Addiction.* 1997;92:207-17. [PMID: 9158232]
  17. Wetter DW, Kenford SL, Smith SS, Fiore MC, Jorenby DE, Baker TB. Gender differences in smoking cessation. *J Consult Clin Psychol.* 1999;67:555-62. [PMID: 10450626]
  18. Stapleton JA, Russell MA, Feyerabend C, Wiseman SM, Gustavsson G, Sawe U, et al. Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction.* 1995;90:31-42. [PMID: 7888977]
  19. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict.* 1991;86:1119-27. [PMID: 1932883]
  20. Westman EC, Behm FM, Simel DL, Rose JE. Smoking behavior on the first day of a quit attempt predicts long-term abstinence. *Arch Intern Med.* 1997;157:335-40. [PMID: 9040302]
  21. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
  22. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. *Obes Res.* 1998;6 Suppl 2:51S-209S. [PMID: 9813653]
  23. Lawson GM, Hurt RD, Dale LC, Offord KP, Croghan IT, Schroeder DR, et al. Application of serum nicotine and plasma cotinine concentrations to assessment of nicotine replacement in light, moderate, and heavy smokers undergoing transdermal therapy. *J Clin Pharmacol.* 1998;38:502-9. [PMID: 9650539]
  24. Jacob P 3rd, Wilson M, Benowitz NL. Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. *J Chromatogr.* 1981;222:61-70. [PMID: 6783675]
  25. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. *Nicotine Tob Res.* 2003;5:13-25. [PMID: 12745503]
  26. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res.* 2002;4:149-59. [PMID: 12028847].
  27. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *Lancet.* 1994;343:139-42. [PMID: 7904003]
  28. Tonnesen P, Norregaard J, Simonsen K, Sawe U. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. *N Engl J Med.* 1991;325:311-5. [PMID: 2057036]
  29. Hjalmarson A, Franzon M, Westin A, Wiklund O. Effect of nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. *Arch Intern Med.* 1994;154:2567-72. [PMID: 7979853]
  30. Paoletti P, Fornai E, Maggiorelli F, Puntoni R, Viegi G, Carrozzi L, et al. Importance of baseline cotinine plasma values in smoking cessation: results from a double-blind study with nicotine patch. *Eur Respir J.* 1996;9:643-51. [PMID: 8726925]
  31. Norregaard J, Tonnesen P, Petersen L. Predictors and reasons for relapse in smoking cessation with nicotine and placebo patches. *Prev Med.* 1993;22:261-71. [PMID: 8483863]
  32. Kenford SL, Fiore MC, Jorenby DE, Smith SS, Wetter D, Baker TB. Predicting smoking cessation. Who will quit with and without the nicotine patch. *JAMA.* 1994;271:589-94. [PMID: 8301790]
  33. Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, et al. Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet.* 1992;340:324-9. [PMID: 1353803]
  34. Prather RD, Tu TG, Rolf CN, Gorsline J. Nicotine pharmacokinetics of Nicoderm (nicotine transdermal system) in women and obese men compared with normal-sized men. *J Clin Pharmacol.* 1993;33:644-9. [PMID: 8366189]
  35. Salamone JD. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behav Brain Res.* 1994;61:117-33. [PMID: 8037860]
  36. Epstein LH, Jaroni JL, Paluch RA, Leddy JJ, Vahue HE, Hawk L, et al. Dopamine transporter genotype as a risk factor for obesity in African-American smokers. *Obes Res.* 2002;10:1232-40. [PMID: 12490667]
  37. Noble EP, St Jeor ST, Ritchie T, Syndulko K, St Jeor SC, Fitch RJ, et al. D2 dopamine receptor gene and cigarette smoking: a reward gene? *Med Hypotheses.* 1994;42:257-60. [PMID: 8072432]
  38. Lerman C, Caporaso NE, Audrain J, Main D, Bowman ED, Lockshin B, et al. Evidence suggesting the role of specific genetic factors in cigarette smoking. *Health Psychol.* 1999;18:14-20. [PMID: 9925041]
  39. Epstein LH, Saelens BE. Behavioral economics of obesity: food intake and energy expenditure. In: Bickel WK, Vuchinich RE, eds. *Reframing Health Behavior Change with Behavioral Economics.* Mahwah, NJ: Lawrence Erlbaum; 2000:293-311.
  40. Piper ME, Fox BJ, Welsh SK, Fiore MC, Baker TB. Gender and racial/ethnic differences in tobacco-dependence treatment: a commentary and research recommendations. *Nicotine Tob Res.* 2001;3:291-7. [PMID: 11767718]
  41. Clark PI, Gautam S, Gerson LW. Effect of menthol cigarettes on biochemical markers of smoke exposure among black and white smokers. *Chest.* 1996;110:1194-8. [PMID: 8915220]
  42. Hymowitz N, Corle D, Royce J, Hartwell T, Corbett K, Orlandi M, et al. Smokers' baseline characteristics in the COMMIT trial. *Prev Med.* 1995;24:503-8. [PMID: 8524726]
  43. Caraballo RS, Giovino GA, Pechacek TF, Mowery PD, Richter PA, Strauss WJ, et al. Racial and ethnic differences in serum cotinine levels of cigarette smokers: Third National Health and Nutrition Examination Survey, 1988-1991. *JAMA.* 1998;280:135-9. [PMID: 9669785]
  44. Perez-Stable EJ, Herrera B, Jacob P 3rd, Benowitz NL. Nicotine metabolism and intake in black and white smokers. *JAMA.* 1998;280:152-6. [PMID: 9669788]
  45. Kiefe CI, Williams OD, Lewis CE, Allison JJ, Sekar P, Wagenknecht LE. Ten-year changes in smoking among young adults: are racial differences explained by socioeconomic factors in the CARDIA study? *Am J Public Health.* 2001;91:213-8. [PMID: 11211629]
  46. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2001:CD000146. [PMID: 11686953]
  47. Fiore MC, Kenford SL, Jorenby DE, Wetter DW, Smith SS, Baker TB. Two studies of the clinical effectiveness of the nicotine patch with different counseling treatments. *Chest.* 1994;105:524-33. [PMID: 8306757]

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