

## THE SAFETY OF TRANSDERMAL NICOTINE AS AN AID TO SMOKING CESSATION IN PATIENTS WITH CARDIAC DISEASE

ANNE M. JOSEPH, M.D., M.P.H., SUZANNE M. NORMAN, PH.D., LINDA H. FERRY, M.D., M.P.H.,  
ALLAN V. PROCHAZKA, M.D., M.Sc., ERIC C. WESTMAN, M.D., M.H.S., BONNIE G. STEELE, R.N., PH.D.,  
SCOTT E. SHERMAN, M.D., M.P.H., MINOT CLEVELAND, M.D., DAVID O. ANTONUCCIO, PH.D.,  
NEIL HARTMAN, M.D., PH.D., AND PAUL G. MCGOVERN, PH.D.

### ABSTRACT

**Background** Transdermal nicotine therapy is widely used to aid smoking cessation, but there is uncertainty about its safety in patients with cardiac disease.

**Methods** In a randomized, double-blind, placebo-controlled trial at 10 Veterans Affairs medical centers, we randomly assigned 584 outpatients (of whom 576 were men) with at least one diagnosis of cardiovascular disease to a 10-week course of transdermal nicotine or placebo as an aid to smoking cessation. The subjects were monitored for a total of 14 weeks for the primary end points of the study (death, myocardial infarction, cardiac arrest, and admission to the hospital due to increased severity of angina, arrhythmia, or congestive heart failure); the secondary end points (admission to the hospital for other reasons and outpatient visits necessitated by increased severity of heart disease); any side effects of therapy; and abstinence from smoking.

**Results** There were 48 primary and 78 secondary end points noted in a total of 95 subjects. At least one of the primary end points was reached by 5.4 percent of the subjects in the nicotine group and 7.9 percent of the subjects in the placebo group (difference, 2.5 percent; 95 percent confidence interval, -1.6 to 6.5 percent;  $P=0.23$ ). In the nicotine group, 11.9 percent of the subjects had at least one of the secondary end points, as compared with 9.7 percent in the placebo group (difference, 2.2 percent; 95 percent confidence interval, -2.2 to 7.4 percent;  $P=0.37$ ). After 14 weeks the rate of abstinence from smoking was 21 percent in the nicotine group, as compared with 9 percent in the placebo group ( $P=0.001$ ), but after 24 weeks the abstinence rates were not significantly different (14 percent vs. 11 percent,  $P=0.67$ ).

**Conclusions** Transdermal nicotine does not cause a significant increase in cardiovascular events in high-risk outpatients with cardiac disease. However, the efficacy of transdermal nicotine as an aid to smoking cessation in such patients is limited and may not be sustained over time. (N Engl J Med 1996; 335:1792-8.)

©1996, Massachusetts Medical Society.

**C**IGARETTE smoking promotes atherosclerosis and is associated with an increased risk of sudden death, myocardial infarction, angina, peripheral vascular disease, and stroke.<sup>1</sup> In patients with cardiac disease who stop smoking, there is a rapid decline in the recurrence of acute cardiovascular events and the

symptoms of atherosclerotic disease.<sup>2</sup> Transdermal nicotine has been shown to be of benefit as an aid to smoking cessation<sup>3</sup> and is a prominent feature of the Clinical Practice Guideline for smoking cessation of the Agency for Health Care Policy and Research.<sup>4</sup> There is ongoing debate, however, about the safety of transdermal nicotine in patients with cardiac disease.<sup>5</sup>

The use of transdermal nicotine in patients with atherosclerotic vascular disease is of concern because some of the cardiotoxic effects of smoking are attributable to nicotine (although some are caused by other components of cigarette smoke). Nicotine has sympathomimetic effects that lead to increases in heart rate and blood pressure<sup>6</sup> and cause coronary vasoconstriction.<sup>7</sup> Components of cigarette smoke other than nicotine contribute to cardiovascular injury by causing the production of carboxyhemoglobin (consequently reducing the delivery of oxygen),<sup>8</sup> increasing platelet aggregation and serum fibrinogen levels,<sup>9</sup> adversely affecting the lipid profile,<sup>10</sup> and promoting oxidant injury<sup>11</sup> and the activation of neutrophils.<sup>12</sup> Treatment with transdermal nicotine, however, generally leads to lower blood nicotine levels than does cigarette smoking,<sup>9</sup> even if the patient continues to smoke during treatment.<sup>13,14</sup> Pharmacologic therapy with nicotine is therefore likely to result in fewer cardiovascular effects than cigarette smoking.

Anecdotal reports of paroxysmal atrial fibrillation,<sup>15-17</sup> myocardial infarction,<sup>18-22</sup> and stroke<sup>23,24</sup> in patients receiving nicotine therapy have made physicians cautious in prescribing nicotine gum or transdermal patches for patients with cardiac disease.<sup>25</sup> Some physicians consider underlying cardiac conditions in patients who smoke as absolute contraindications

From the Department of Medicine, Veterans Affairs (VA) Medical Center and University of Minnesota, Minneapolis (A.M.J.); the Department of Psychology, VA Medical Center, Kansas City, Mo. (S.M.N.); the Department of Medicine, VA Medical Center, Loma Linda, Calif. (L.H.F.); the Department of Medicine, VA Medical Center, Denver (A.V.P.); the Department of Medicine, VA Medical Center, Durham, N.C. (E.C.W.); the Nursing Service, VA Medical Center, Seattle (B.G.S.); the Primary Ambulatory Care and Education Center, VA Medical Center, Sepulveda, Calif. (S.E.S.); the Department of Medicine, VA Medical Center, Portland, Ore. (M.C.); the Psychology Service, VA Medical Center, Reno, Nev. (D.O.A.); the Department of Psychiatry, VA Medical Center, Los Angeles (N.H.); and the Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis (P.G.M.). Address reprint requests to Dr. Joseph at the Section of General Internal Medicine (111-0), Veterans Affairs Medical Center, 1 Veterans Dr., Minneapolis, MN 55417.

tions to nicotine therapy, although others prescribe reduced doses. Reports in the press of adverse events have made some patients leery of nicotine therapy and may have deterred attempts to quit smoking.<sup>21</sup> The Food and Drug Administration has recently approved transdermal nicotine for sale over the counter, which makes it imperative to determine the drug's safety in patients with cardiovascular disease. Our study was a randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the safety and efficacy of transdermal nicotine as an aid to smoking cessation in cigarette smokers with at least one major cardiovascular disorder.

## METHODS

### Participants

#### *Inclusion Criteria*

In 10 Veterans Affairs medical centers (VAMCs), we enrolled smokers, 45 years of age or older, who smoked at least 15 cigarettes per day. The subjects must have smoked for at least five years, made a minimum of two previous attempts to quit, and had a level of carbon monoxide in expired air of more than 8 parts per million (ppm). All subjects had one or more of the following diagnosed conditions: a history of myocardial infarction, a history of coronary-artery bypass surgery or angioplasty, stenosis of at least 50 percent in at least one major coronary artery as seen with coronary angiography, or a clinical history of angina, congestive heart failure, cor pulmonale, arrhythmia, peripheral vascular disease, or cerebrovascular disease.

#### *Exclusion Criteria*

Criteria for exclusion were any of the following in the two weeks before randomization: unstable angina, myocardial infarction, coronary-artery bypass surgery, angioplasty, or hospitalization for cardiac arrhythmia. A history of continuous use of transdermal nicotine for more than 48 hours, current use of (and an unwillingness to stop using) other tobacco products or nicotine gum, the presence of unstable psychiatric illness or an unstable disorder involving the use of alcohol or controlled substances, a history of severe dermatitis, and pregnancy were additional exclusion criteria.

### Randomization and Treatment

The Minneapolis VAMC Coordinating Center used a computer-generated schedule to randomly assign patients to the study groups in blocks of 10. The protocol was approved by the institutional review boards at all 10 sites. Potential subjects were advised that they would be told to quit smoking one day after randomization.

#### *Pharmacologic Treatment*

The treatment protocol prescribed transdermal nicotine (Nicoderm, Hoechst Marion Roussel) given as a 21-mg patch for 6 weeks, a 14-mg patch for 2 weeks, and a 7-mg patch for 2 weeks, for a total course of treatment of 10 weeks. Subjects in the placebo group were given placebo patches of identical size, appearance, and odor. All subjects were instructed to apply a new patch each morning after removing the old patch, and to place the patch in a different position each day to avoid skin irritation.

#### *Other Treatment*

Subjects returned to the hospital for outpatient visits at the end of the 1st, 6th, and 14th weeks. They received the National Cancer Institute's pamphlets "Clearing the Air"<sup>26</sup> and "Why Do You

Smoke?"<sup>27</sup> at the base-line visit. Subjects were instructed not to smoke while wearing patches. They received brief behavioral counseling, by either the principal investigator or the study coordinator, which lasted for 15 minutes at the base-line visit and for 10 minutes at each of the next two visits (week 1 and week 6).

#### *Deviations from the Protocol*

If at the week 6 visit subjects reported having smoked more than five cigarettes in the previous week or had a carbon monoxide level in expired air of more than 8 ppm, the patch treatment was discontinued. Subjects with symptoms of nicotine toxicity (including diarrhea, abdominal pain, vomiting, dizziness, and headache) that were rated as severe had their dose decreased from 21 mg to 14 mg. These subjects received an accelerated and shortened course of treatment after the first reduced dose: 14 mg for two weeks and 7 mg for two weeks. If their only severe symptom was sleep disturbance, subjects were instructed to remove the 21-mg patch at night, but otherwise they kept receiving treatment according to the protocol.

### Data Collection

Information on the subjects' employment status, education, smoking behavior (the nicotine content of their usual brands of cigarettes as calculated with the Federal Trade Commission's smoking-machine method<sup>28</sup> and the responses to the Fagerström Tolerance Questionnaire<sup>29</sup>), and medical history, as well as the smoking status of household members, was collected at the base-line visit. The subjects kept weekly diaries of their patch use, the number of cigarettes smoked, any symptoms of nicotine withdrawal or toxicity, and the number of visits made to health care providers. At each scheduled study visit the subjects returned the diaries as well as all used and unused patches, which were counted. At all 10 sites the level of expired carbon monoxide was measured with Bedfont Micro Smokerlyzers (Bedfont Scientific). The subjects were instructed to hold their breath for 15 seconds before exhaling into the meter.

### Outcome Measures

#### *Safety*

The subjects reported adverse events in their weekly diaries and at scheduled study visits, and study personnel also reviewed the hospitals' computerized patient records to ascertain and verify end points (e.g., hospitalization).

Adverse events were classified as mild, moderate, or serious. Serious adverse events were further classified a priori into three groups of end points. Primary end points were death, myocardial infarction, cardiac arrest, and admission to the hospital due to increased severity of angina, arrhythmia, or congestive heart failure. Secondary end points were admission due to peripheral vascular disease, cerebrovascular disease, or other indications and outpatient visits necessitated by the increased severity of atherosclerotic cardiac diseases (angina, arrhythmia, or congestive heart failure). The third category of end points consisted of potential side effects of therapy with transdermal nicotine, such as sleep disturbance, a skin reaction, gastrointestinal distress, and miscellaneous other symptoms that were rated as severe and required adjustment of the patient's dose. Predetermined criteria were used to evaluate the relation of administration of the drug to an adverse event; either the drug and the event were considered not related or the relation was classified as remote, possible, probable, or definite.

#### *Efficacy*

Abstinence was defined as the subject's not having smoked for at least 8 weeks, as verified at the end of the 14th week after randomization by a level of expired carbon monoxide of 10 ppm or less. At 24 weeks, subjects who reported by telephone that they had not smoked, and who underwent a confirmatory measure-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY GROUPS.**

CHARACTERISTIC	NICOTINE (N = 294)	PLACEBO (N = 290)
<b>Medical history</b>		
Age — yr	61	60
Inclusion criteria — no. (%)*		
History of myocardial infarction	120 (41)	112 (39)
History of coronary-artery bypass grafting or angioplasty	111 (38)	92 (32)
Stenosis $\geq 50\%$ in $\geq 1$ coronary arteries	22 (7)	41 (14) <sup>†</sup>
Clinical history of angina	105 (36)	106 (37)
Congestive heart failure	34 (12)	40 (14)
Cor pulmonale	3 (1)	2 (1)
Arrhythmia	43 (15)	43 (15)
Peripheral vascular or cerebrovascular disease	96 (33)	102 (35)
<b>Base-line severity of cardiac disease</b>		
Angina at base line — no. (%)	145 (49)	128 (44)
Average no. of episodes/wk	2.1	2.5
No. of nitroglycerin tablets/wk	1.8	1.5
CCS classification — no. (%) <sup>‡</sup>		
Class I	82 (59)	69 (54)
Class II	39 (28)	43 (34)
Class III	15 (11)	11 (9)
Class IV	3 (2)	4 (3)
<b>Physical examination</b>		
Weight — kg	86.4	88.2
Systolic blood pressure — mm Hg	137	136
Diastolic blood pressure — mm Hg	78	79
Pulse — beats/min	75	76
<b>Smoking history</b>		
No. of cigarettes/day	28	28
Duration of smoking — yr	44	44
Previous attempts to quit — no. (%)		
2–5 attempts	184 (63)	181 (62)
>5 attempts	110 (37)	109 (38)
Nicotine content of usual brand of cigarettes $\leq 0.9$ mg — no. (%) <sup>§</sup>	140 (49)	145 (50)
Fagerström score <sup>¶</sup>	6.4	6.4
Expired carbon monoxide — ppm	25	25

\*Subjects may have multiple diagnoses.

<sup>†</sup>P = 0.01 for the comparison between groups.

<sup>‡</sup>Canadian Cardiovascular Society (CCS) class I indicates that ordinary activity does not cause angina but angina occurs with strenuous work; class II denotes a slight limitation of ordinary activity; class III, a marked limitation of ordinary physical activity; and class IV, inability to carry on any physical activity without discomfort. CCS classifications were available for 139 subjects in the nicotine group and 127 subjects in the placebo group.

<sup>§</sup>These data are based on 288 subjects in the nicotine group and 287 subjects in the placebo group.

<sup>¶</sup>The range for the Fagerström score is 0 through 11; 11 indicates the greatest nicotine dependence.

ment of their level of expired carbon monoxide, were considered abstinent.

### Statistical Analysis

Sample size was calculated on the basis of a rate of approximately 15 percent for the combined end points in the control group, the rate observed in a pilot study.<sup>14</sup> We therefore planned to enroll approximately 580 subjects in order to have a power of 0.9 (alpha, 0.05; one-sided analysis) to detect an increase of 10 percentage points in the rate of adverse events due to treatment. The nicotine and placebo groups were compared with respect to

a large number of base-line variables involving the subjects' medical history, severity of cardiac disease, history of smoking, and the results of physical examination. Analysis of variance was used for continuous variables, and chi-square analysis was used for categorical variables. Analyses were conducted both according to subject and according to event, because some subjects had more than one event and the events were not independent. The most serious adverse event for each subject who had more than one event was used for analysis. We cross-classified serious events according to the original group assignment (intention to treat), among subjects who wore nicotine patches according to the protocol, and according to smoking status. All data analyses were performed with SAS software.<sup>30</sup>

## RESULTS

### Characteristics of the Study Subjects

We enrolled 584 subjects in the trial, 8 of whom were women, between November 28, 1994, and June 30, 1995. The subjects were on average 60 years of age (range, 45 to 82). From 24 to 116 subjects were enrolled at each site.

### Medical History and Physical Examination

The most common reasons for inclusion in the study were a history of myocardial infarction (40 percent of the subjects), a history of coronary-artery bypass surgery or angioplasty (35 percent), a clinical history of angina (36 percent), and the presence of peripheral vascular disease (34 percent). Other medical conditions common among the subjects were hypertension (35 percent), chronic obstructive pulmonary disease (21 percent), diabetes (17 percent), depression (11 percent), peptic ulcer disease (10 percent), other psychiatric conditions (9 percent), and a history of a substance-use disorder (6 percent).

Commonly used medications included anticoagulants (used by 11 percent of the subjects), opioid analgesics (14 percent), antidepressants (15 percent), digitalis (14 percent), beta-blockers (23 percent), calcium-channel blockers (29 percent), nitrates (45 percent), antiarrhythmic agents (2 percent), lipid-lowering agents (13 percent), diuretics (19 percent), angiotensin-converting-enzyme inhibitors (24 percent), histamine antagonists (24 percent), hypoglycemic agents (12 percent), and therapeutic drugs for chronic obstructive pulmonary disease (18 percent). There were no significant differences in medication use between the nicotine group and the placebo group.

Patients in both study groups who reported angina at base line had an average of two episodes per week and took an average of almost two sublingual nitroglycerin tablets per week. The majority of subjects were in Canadian Cardiovascular Society (CCS) class I (that is, they reported having angina only with strenuous work). Measurements of weight, blood pressure, and pulse were similar in the two groups (Table 1).

**Smoking History**

On average, subjects reported smoking 28 cigarettes per day at base line and had smoked for 44 years. For 86 percent of the subjects, the delivered nicotine content of their usual brand of cigarettes was less than 1.2 mg. The average score on the Fagerström Tolerance Questionnaire was 6.4 and the base-line level of expired carbon monoxide was 25 ppm in both the nicotine and placebo groups (Table 1).

**Outcome Measures**

There were 48 primary and 78 secondary end points observed in a total of 95 of the study subjects. In the nicotine group, 5.4 percent (16 subjects) had primary end points, as compared with 7.9 percent of the placebo group (23 subjects) (difference, 2.5 percent; 95 percent confidence interval,  $-1.6$  to  $6.5$  percent;  $P=0.23$ ) (Table 2). The distribution of primary end points was similar in the two groups, with the exception of deaths, which were more common in the placebo group. However, that difference did not reach statistical significance ( $P=0.07$ ).

There were no significant differences between groups in the occurrence of secondary end points (nicotine group, 11.9 percent; placebo group, 9.7

percent; difference, 2.2 percent; 95 percent confidence interval,  $-2.2$  to  $7.4$  percent;  $P=0.37$ ). More subjects in the nicotine group (12) than in the placebo group (7) had outpatient visits for chest pain, arrhythmia, or congestive heart failure ( $P=0.5$ ). In both study groups, 16 percent of the subjects had either a primary or a secondary end point (nicotine group, 16.3 percent; placebo group, 16.2 percent; difference, 0.1 percent; 95 percent confidence interval,  $-5.9$  to  $6.1$  percent;  $P=0.97$ ) (Table 2).

**Use of Patches at the Time of Events**

Because some subjects discontinued therapy on their own, we also analyzed the data considering only subjects who used patches according to the study protocol. At the week 6 visit, 73 percent of the subjects in the nicotine group were wearing patches, as compared with 56 percent in the placebo group ( $P=0.004$ ). In this analysis, 15.3 percent of the nicotine group (29 subjects) had primary or secondary end points, as compared with 11.6 percent of the placebo group (20 subjects) ( $P=0.48$ ). There were 39 primary and secondary end points in the nicotine group, as compared with 27 end points in the placebo group ( $P=0.86$ ).

**TABLE 2.** SERIOUS ADVERSE EVENTS ACCORDING TO STUDY GROUP.

EVENT	SUBJECTS WITH EVENTS*			EVENTS		
	NICOTINE (N=294)	PLACEBO (N=290)	P VALUE	NICOTINE	PLACEBO	P VALUE
	no. (%)			no.		
Primary end points						
Death	1	6		1	6	
Myocardial infarction	0	1		0	1	
Cardiac arrest	1	1		1	1	
Admission for increased severity of angina	7	10		8	12	
Admission for arrhythmia	5	3		6	6	
Admission for congestive heart failure	2	2		3	3	
Total	16 (5.4)	23 (7.9)	0.23	19	29	0.10
Secondary end points						
Admission for peripheral vascular disease	3	5		3	5	
Admission for cerebrovascular disease	4	3		5	4	
Admission for other reasons†	16	13		21	16	
Outpatient visit for increased severity of atherosclerotic cardiovascular disease	12	7		16	8	
Total	35 (11.9)	28 (9.7)	0.37	45	33	0.23
All end points	48 (16.3)	47 (16.2)	0.97	64	62	0.39

\*If subjects had both a primary and a secondary end point, they were counted once in each of those two general categories. Therefore, the total number of subjects with any end point in each study group is less than the sum of the subjects with primary and secondary end points. If subjects had more than one primary end point or more than one secondary end point, they were counted only once in a general category, under the most serious primary or secondary end point.

†"Other reasons" includes admissions for chronic obstructive pulmonary disease, upper gastrointestinal bleeding, hemoptysis, pneumonia, deep venous thrombosis, hyperglycemia, otitis, pulmonary nodule, hernia repair, renal stone, pulmonary embolus, or colon cancer.

**TABLE 3. SUBJECTS' SMOKING STATUS AT THE TIME OF SERIOUS ADVERSE EVENTS, ACCORDING TO STUDY GROUP.\***

EVENT	NICOTINE		PLACEBO	
	NOT SMOKING	SMOKING	NOT SMOKING	SMOKING
	no. of subjects			
Primary end points				
Death	0	1	0	3
Myocardial infarction	0	0	0	1
Cardiac arrest	1	0	1	0
Admission for increased severity of angina	3	4	4	5
Admission for arrhythmia	1	4	0	3
Admission for congestive heart failure	2	0	1	1
Total	7	9	6	13
Secondary end points				
Admission for peripheral vascular disease	1	1	1	3
Admission for cerebrovascular disease	1	3	0	2
Admission for other reasons†	6	6	2	9
Outpatient visit for increased severity of atherosclerotic cardiovascular disease	4	7	0	5
Total	12	17	3	19
All end points	19	26	9	32

\*Subjects who had smoked at least one cigarette within the three days before the event were classified as smoking; this analysis includes only events for which the smoking status of the subject was known. Only the most serious event in a subject was included in this analysis (45 events in the nicotine group and 41 in the placebo group).

†“Other reasons” includes admissions for chronic obstructive pulmonary disease, upper gastrointestinal bleeding, hemoptysis, pneumonia, deep venous thrombosis, hyperglycemia, otitis, pulmonary nodule, hernia repair, renal stone, pulmonary embolus, or colon cancer.

**TABLE 4. SEVERE SIDE EFFECTS OF TRANSDERMAL NICOTINE THERAPY, ACCORDING TO STUDY GROUP.**

SIDE EFFECT	SUBJECTS WITH EVENTS*			EVENTS		
	NICOTINE (N=294)	PLACEBO (N=290)	P VALUE	NICOTINE	PLACEBO	P VALUE
	no. (%)			no.		
Sleep disturbance	10	6		10	6	
Skin reaction	6	3		6	4	
Gastrointestinal distress	5	6		6	7	
Other†	15	12		18	13	
Total	36 (12.2)	27 (9.3)	0.25	40	30	0.24

\*Some subjects had more than one event.

†“Other” includes dizziness, dry mouth, sweating, malaise, and influenza-like symptoms.

**Smoking Status at the Time of Events**

Smoking status at the time of an end point was reported for 86 of the 95 subjects who had primary or secondary end points. At the time of 45 primary and secondary events in the nicotine group, 19 subjects (42 percent) were abstaining from smoking and 26 (58 percent) were smoking; at the time of 41 events in the placebo group, 9 subjects (22 percent) were abstaining from smoking and 32 (78 percent) were still smoking ( $P=0.05$ ) (Table 3). We also compared the occurrence of end points in 294 subjects in the nicotine group according to their smoking status at 14 weeks. Nine percent of the abstinent subjects had primary end points, as compared with 5 percent of those who were still smoking, and 13 percent had secondary end points, as compared with 10 percent of subjects still smoking ( $P=0.29$  for a combined primary and secondary end point).

**Side Effects of Transdermal Nicotine**

The distribution of side effects commonly attributed to nicotine patches, such as sleep disturbance, skin reactions, and gastrointestinal distress, was similar in the two study groups (Table 4).

The principal investigator at each site assessed the relation of administration of the study drug to study

end points and potential side effects of therapy with transdermal nicotine; the drug was considered to be not related or only remotely related to the event in 64 percent of adverse events (92 of 143), possibly related in 20 percent of events (29), probably related in 9 percent of events (13), and definitely related in 6 percent of events (9). There were no significant differences in these rates between the nicotine group and the placebo group. There were also no differences according to study group in the rates of dose adjustment, discontinuation of medication, or the addition of medication necessitated by an adverse event.

#### Physical Examination

Subjects in the nicotine group gained an average of 1.4 kg between base line and the 14th week, as compared with 0.3 kg in subjects receiving placebo ( $P=0.001$ ). Changes in systolic and diastolic blood pressure and pulse were negligible in both study groups.

#### Efficacy

At 14 weeks after randomization, 21 percent of the subjects in the nicotine group and 9 percent in the placebo group were abstaining from smoking, as confirmed by the measurement of expired carbon monoxide ( $P=0.001$ ). However, at 24 weeks, 14 percent of the subjects in the nicotine group, as compared with 11 percent in the placebo group, were abstaining ( $P=0.67$ ).

### DISCUSSION

This multicenter study showed that serious adverse events are common and occur at nearly the same rate among subjects with cardiovascular disease who try to quit smoking, regardless of whether they use transdermal nicotine or placebo. In our study, the proportion of primary end points was greater in the placebo group, but the proportion of secondary end points was greater in the nicotine group. Neither of these differences, however, was statistically significant. There was no increase in death, myocardial infarction, or arrhythmia associated with transdermal nicotine, regardless of whether the data were analyzed according to the intention to treat or according to the actual use of patches. Symptoms commonly attributed to treatment with nicotine patches, such as sleep disturbance, skin reactions, and gastrointestinal distress, were equally common in both study groups.

These findings are consistent with a previous study assessing therapy with transdermal nicotine in patients with cardiac disease.<sup>5</sup> Those investigators conducted a five-week, placebo-controlled trial, with a lower dose of transdermal nicotine (14 mg) than the one we used, in 156 patients with documented atherosclerotic cardiovascular disease. One subgroup of patients underwent extensive monitoring, including 24-hour electrocardiography. There was no differ-

ence between the treatment and placebo groups in the frequency of angina.<sup>5</sup> In our study, intervention was less efficacious than it was in trials of intervention to stop smoking among inpatients with acute cardiac disease; in those trials, success rates were unusually high, even without the use of pharmacologic therapy.<sup>31-34</sup> A high prevalence of coexisting psychiatric conditions in the population we were studying and a history of numerous past failures to quit smoking may explain this finding.

The finding of multiple adverse events in the control group in our study brings a new perspective to published case reports of cardiac events among patients receiving nicotine-replacement therapy.<sup>15-25</sup> These previous reports have stressed the importance of concurrent patch use and smoking. Our data, however, show that more adverse events occurred in subjects wearing placebo patches who smoked during treatment than in subjects wearing active patches who smoked, and they show no increase in events among smokers as compared with nonsmokers (although the subjects in this analysis were not randomly assigned). Several factors are important in evaluating the risk of using patches without abstaining from smoking: the effect of nicotine treatment, the effect of nicotine withdrawal, and the number of cigarettes subjects continue to smoke. Having smoked in the three days before an adverse event may result in cardiotoxic effects that are not related to nicotine, such as a hypercoagulable state that can persist approximately one week after smoking.<sup>35</sup>

The limitations of our study include the facts that it was almost completely restricted to male veterans and that it was not possible to verify the smoking status of the subjects at the time of the occurrence of adverse events. Given our sample size we cannot exclude the possibility of an approximately 5 percent increase in primary and secondary end points due to treatment, or of small differences in the long-term rates of smoking cessation. This small potential risk should be considered in the context of the known benefits of smoking cessation in patients with cardiovascular disease.

It should not be expected that therapy with transdermal nicotine would increase the risk of adverse events in patients with cardiac disease according to the dose of nicotine delivered. Plasma nicotine levels, even in patients using full-dose transdermal delivery systems, are likely to be lower than those of the average smoker.<sup>36</sup> On average, patch users who continue smoking smoke fewer cigarettes.<sup>13</sup> In addition, the flattening out of the dose-response curve for the cardiac effects of nicotine provides a safeguard against effects associated with slight elevations in nicotine levels, should they occur.<sup>37</sup> Moreover, smoking causes a rapid rise in plasma nicotine levels, with higher peak levels in arterial blood than in venous blood; patches, by contrast, effect a gradual

rise in nicotine levels and only minimal arterial-venous differences.<sup>38</sup> Therefore, transdermal nicotine is likely to be safer for the cardiovascular system than inhaled nicotine, because the relatively stable blood nicotine levels associated with the patches sustain the body's tolerance with respect to the drug's sympathomimetic effects.

It is advisable to caution all patients not to smoke while using patches; studies of cessation demonstrate that even occasional smoking during replacement therapy is predictive of long-term failure to quit smoking.<sup>39</sup> Provided there is still a reasonable chance that patients can manage to abstain from tobacco, however, our data do not demonstrate a need for instructing them to stop patch use immediately if they "slip" and smoke during treatment.

These data suggest that concern about the use of nicotine-replacement therapy for smokers with cardiovascular disease is not warranted. Nicotine has pharmacologic effects that may contribute to cardiotoxicity, but transdermal nicotine therapy is likely to be less dangerous to a patient than smoking, because it does not increase thrombogenesis, decrease oxygen-carrying capacity, or lead to atherogenesis. Because the majority of patients with cardiac disease, peripheral vascular disease, and cerebrovascular disease have been given repeated advice to stop smoking but have still been unsuccessful in numerous attempts, every safe technique should be made available to help them quit, including the use of transdermal nicotine.

Supported by a grant from Hoechst Marion Roussel.

*We are indebted to Helen Roemhild, Pam Werb, and the study coordinators at all the sites for their assistance in the recruitment of subjects and the conduct of this trial; and to the members of the Data and Safety Monitoring Board: Dr. Frank Lederle, Dr. Gordon Pierpont, and Dr. Dorothy Hatsukami.*

## REFERENCES

- Department of Health and Human Services. The health consequences of smoking: cardiovascular disease: a report of the Surgeon General. Washington, D.C.: Government Printing Office, 1983. (DHHS publication no. (PHS) 84-50204.)
- Idem*. The health benefits of smoking cessation: a report of the Surgeon General. Washington, D.C.: Government Printing Office, 1990. (DHHS publication no. (CDC) 90-8416.)
- 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.
- Fiore MC, Bailey WC, Cohen SJ, et al. Smoking cessation: clinical practice guideline no. 18. Washington, D.C.: Government Printing Office, 1996. (AHCPR publication no. 96-0692.)
- Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med* 1994;154:989-95.
- Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. *N Engl J Med* 1984;319:1318-30.
- Kajiser L, Berglund B. Effect of nicotine on coronary blood-flow in man. *Clin Physiol* 1985;5:541-52.
- Allred EN, Bleecker ER, Chaitman BR, et al. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 1989;321:1426-32. [Erratum, *N Engl J Med* 1990;322:1019.]
- Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *J Am Coll Cardiol* 1993;22:1159-67.
- Allen SS, Hatsukami D, Gorsline J. Cholesterol changes in smoking cessation using the transdermal nicotine system: Transdermal Nicotine Study Group. *Prev Med* 1994;23:190-6.
- Morrow JD, Frei B, Longmire AW, et al. Increase in circulating products of lipid peroxidation (F<sub>2</sub>-isoprostanes) in smokers: smoking as a cause of oxidative damage. *N Engl J Med* 1995;332:198-203.
- Gillum RF, Ingram DD, Makuc DM. White blood cell count and stroke incidence and death: the NHANES I epidemiologic follow-up study. *Am J Epidemiol* 1994;139:894-902.
- Transdermal Nicotine Study Group. Transdermal nicotine for smoking cessation: six-month results from two multicenter controlled clinical trials. *JAMA* 1991;266:3133-8.
- Joseph AM, Westman EC. Transdermal nicotine therapy for older, medically ill patients: a pilot study. *J Gen Intern Med* 1995;10:Suppl:101. abstract.
- Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. *JAMA* 1994;272:1497-505.
- Rigotti NA, Eagle KA. Atrial fibrillation while chewing nicotine gum. *JAMA* 1986;255:1018.
- Stewart PM, Catterall JR. Chronic nicotine ingestion and atrial fibrillation. *Br Heart J* 1985;54:222-3.
- Dacosta A, Guy JM, Tardy B, et al. Myocardial infarction and nicotine patch: a contributing or causative factor? *Eur Heart J* 1993;14:1709-11.
- Warner JG Jr, Little WC. Myocardial infarction in a patient who smoked while wearing a nicotine patch. *Ann Intern Med* 1994;120:695.
- Ottervanger JP, Festen JM, de Vries AG, Stricker BH. Acute myocardial infarction while using the nicotine patch. *Chest* 1995;107:1765-6.
- Hwang SL, Waldholt M. Heart attacks reported in patch users still smoking. *Wall Street Journal*. June 19, 1992:B1.
- Fredrickson PA, Hurt RD, Lee GM, et al. High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology* 1995;122:215-22.
- Pierce JR Jr. Stroke following application of a nicotine patch. *Ann Pharmacother* 1994;28:402.
- Jackson M. Cerebral arterial narrowing with nicotine patch. *Lancet* 1993;342:236-7.
- Arnaot MR. Treating heart disease: nicotine patches may not be safe. *BMJ* 1995;310:663-4.
- Clearing the air: how to quit smoking . . . and quit for keeps. Bethesda, Md.: National Cancer Institute, 1993. (NIH publication no. 95-1647.)
- Why do you smoke? Bethesda, Md.: National Cancer Institute, 1993. (NIH publication no. 94-1822.)
- Tar, nicotine and carbon monoxide content of the smoke of 475 varieties of domestic cigarettes. Washington, D.C.: Federal Trade Commission, 1991.
- Fagerström KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerström Tolerance Questionnaire. *J Behav Med* 1989;12:159-82.
- SAS/STAT user's guide, version 6. 4th ed. Vols. 1 and 2. Cary, N.C.: SAS Institute, 1989.
- Taylor CB, Houston-Miller N, Killen JD, DeBusk RF. Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. *Ann Intern Med* 1990;113:118-23.
- Rigotti NA, McKool KM, Shiffman S. Predictors of smoking cessation after coronary artery bypass graft surgery: results of a randomized trial with 5-year follow-up. *Ann Intern Med* 1994;120:287-93.
- DeBusk RF, Miller NH, Superko HR, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med* 1994;120:721-9.
- Frid D, Ockene IS, Ockene JK, et al. Severity of angiographically proven coronary artery disease predicts smoking cessation. *Am J Prev Med* 1991;7:131-5.
- FitzGerald GA, Oates JA, Nowak J. Cigarette smoking and hemostatic function. *Am Heart J* 1988;115:267-71.
- Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med* 1995;333:196-203.
- Benowitz NL, Jacob P III. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. *J Pharmacol Exp Ther* 1990;254:1000-5.
- Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend* 1993;33:23-9.
- 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.

**CORRECTION**

**The Safety of Transdermal Nicotine as an Aid to Smoking Cessation in Patients with Cardiac Disease and Lack of Efficacy of Transdermal Nicotine in Smoking Cessation**

The Safety of Transdermal Nicotine as an Aid to Smoking Cessation in Patients with Cardiac Disease and Lack of Efficacy of Transdermal Nicotine in Smoking Cessation and Lack of Efficacy of Transdermal Nicotine in Smoking Cessation . Dr. David O. Antonuccio's name was misspelled in both articles (page 1792 of the 1996 article and page 1157 of the 1999 letter). We regret the errors. The text has been corrected on the *Journal's* Web site at [www.nejm.org](http://www.nejm.org).