

Nicotine Inhaler and Nicotine Patch as a Combination Therapy for Smoking Cessation

A Randomized, Double-blind, Placebo-Controlled Trial

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Background: Nicotine replacement therapy is an effective treatment for nicotine-dependent smokers. However, cessation rates are modest, and preliminary studies suggest that combination therapy may be superior. We compared the efficacy of the nicotine inhaler plus nicotine patch vs nicotine inhaler plus placebo patch for smoking cessation.

Methods: A double-blind, randomized, placebo-controlled trial was conducted in 400 subjects who had smoked 10 or more cigarettes per day for 3 years or longer. Group 1 (n=200) received the nicotine inhaler plus nicotine patch (delivering 15 mg of nicotine per 16 hours) for 6 weeks, then inhaler plus placebo patch for 6 weeks, then inhaler alone for 14 weeks. Group 2 (n=200) received the nicotine inhaler plus placebo patch for 12 weeks, then inhaler for 14 weeks. Inhaler was used at a rate of 6 to 12 cartridges per day ad libitum for 3 months and then tapered off. Main outcome measures were complete abstinence (self-reported) and expired carbon dioxide concentration less than 10 ppm.

Results: Group 1 vs group 2 complete abstinence rates were 60.5% and 47.5% at 6 weeks ($P=.009$), 42.0% and 31.0% at 12 weeks ($P=.02$), 25.0% and 22.5% at 6 months ($P=.56$), and 19.5% and 14.0% at 12 months ($P=.14$). One-year survival analysis showed a significant association between abstinence and treatment with nicotine inhaler plus nicotine patch ($P=.04$). Mean nicotine substitution at week 6 was 60.1% (group 1) and 24.6% (group 2) ($P<.001$). At 12 months, the frequency of respiratory symptoms in abstinent subjects fell significantly and lung function showed a trend toward improvement. The most common adverse events were throat irritation (inhaler) and itching (patch).

Conclusions: Treatment with the nicotine inhaler plus nicotine patch resulted in significantly higher cessation rates than inhaler plus placebo patch.

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TOBACCO SMOKING is responsible for 3 million deaths per year worldwide.¹ In a 40-year follow-up study on smoking and death among British physicians, Doll and colleagues² observed an excess mortality, largely because of smoking-related diseases, which was twice as high during the second half of the study (1971-1991) as it had been during the first half (1951-1971). Importantly, those who stopped smoking before middle age were subsequently found to avoid almost all of the excess risk that they would otherwise have suffered; similarly, those who stopped smoking in middle age were subsequently found to be at less risk than those who continued to smoke. Such findings illustrate the value of smoking cessation in the fight against smoking-induced diseases.

It is now accepted that the addictive nature of cigarette smoking results from

dependence on nicotine,³ and this underlies the rationale for the use of nicotine replacement therapy (NRT) to aid smoking cessation. Delivery of nicotine by means of chewing gum (nicotine polacrilex)⁴⁻⁷ has been shown to be effective in achieving sustained abstinence. However, one potential disadvantage is that, to achieve effective therapeutic blood nicotine levels, subjects need to use a sufficient number of pieces of gum to prevent underdosing.⁸ A simpler, more discreet method is the nicotine transdermal patch, which only needs to be applied once a day.⁹⁻¹² A meta-analysis by Fiore and colleagues¹³ showed the nicotine patch to be a consistently effective aid to smoking cessation; quit rates with the active patch were double those with placebo, and this result appeared to be independent of behavioral counseling or weaning. An alternative method of administering nicotine is via an oral inhaler, in which air is saturated with nico-

SUBJECTS AND METHODS

RANDOMIZATION

Subjects from Nancy, France, and surrounding towns were recruited by means of a local newspaper. The first subject was enrolled in March 1996, and follow-up was completed in February 1998. Of approximately 1000 people who contacted the Centre Hospitalier Universitaire de Nancy-Brabois, 462 underwent a prospective telephone screen to enroll 400 subjects who met the inclusion criteria. To be eligible for the study, subjects had to be aged 18 to 70 years, to have smoked 10 or more cigarettes per day for 3 or more years, to have an expired carbon monoxide level of 10 ppm or more, to have made 1 or more previous attempts to quit, to be personally motivated to stop smoking, and to be fluent in French.

Exclusion criteria included a history of myocardial infarction within the past 3 months; unstable angina; severe cardiac arrhythmia; serious renal, pulmonary, endocrine, or neurological disorders; pregnancy or breastfeeding; and use of any form of smokeless tobacco or nicotine substitution. Subjects who had followed any smoking cessation program during the past 6 months, alcoholics or illegal drug users, those using psychoactive drugs, and those with generalized dermatological diseases were also excluded.

Subjects who fulfilled the entry criteria attended an appointment 1 week later, during which they completed various questionnaires and baseline biological and pulmonary function assessments were performed. All subjects were given complete verbal and written instructions regarding the general conduct of the study, and proper use of the medication was demonstrated. At every visit, only brief counseling and support were provided by the investigator.

All patients gave informed consent, and the study protocol was approved by the local ethics committee of Meurthe-et-Moselle, France.

STUDY DESIGN AND MEDICATION

Subjects were assigned to 1 of 2 treatment groups according to a computer-generated randomization code: 200 subjects were assigned to receive a combination of the nicotine inhaler plus nicotine patch (group 1) and 200 to receive the nicotine inhaler plus placebo patch (group 2). Sealed randomization envelopes were provided for each subject and were held by the hospital pharmacy, which was responsible for dispensing medication.

All medications were supplied by Pharmacia & Upjohn Consumer Healthcare, Helsingborg, Sweden. The nicotine inhaler is a plastic tube containing a perforated plastic plug impregnated with 10 mg of nicotine, approximately 4 mg of which is available for inhalation, and an additive (menthol) to reduce the irritant effect of nicotine. Subjects were instructed to puff shallowly about 10 times more often than when smoking a cigarette (100 puffs during 20 minutes was expected to approximate 10 puffs from 1 cigarette smoked during 5 minutes), as shallow puffing reduces the likelihood of throat irritation. Subjects were instructed not to use the inhaler below 15°C, as this could reduce nicotine delivery. The 30-cm² nicotine patch contained 0.83 mg of nicotine per square centimeter, delivering 15 mg per 16 hours. The placebo patch was the same size and appearance but did not contain nicotine. The study was double blind up to week 6, single blind from weeks 6 to 12, and open thereafter.

Seven visits were arranged: the day before quit day, after 1, 2, 6, and 12 weeks, and at 6 and 12 months (**Table 1**). The total treatment period (including tapering) was 26 weeks. From quit day to week 6, participants in group 1 received the nicotine inhaler plus the nicotine patch, whereas those in group 2 received the nicotine inhaler plus placebo patch. From weeks 7 to 12, subjects in group 1 received the placebo patch instead of the nicotine patch, while group 2 treatment remained unchanged. Both groups received identical treatment (placebo) during this period, to evaluate whether discontinuation of transdermal nicotine administration during double-blind conditions would result in relapse. During the first 3 months, subjects were recommended to use 6 to 12 inhaler cartridges per day ad libitum. Subjects were instructed to use a new inhaler if they believed that the previous one had become inactive; inhalers were considered inactive after 60 minutes of continuous use (300-400 puffs), after 2 hours if opened, or if the subject believed the existing inhaler had lost its effect. At the end of month 3, the placebo patch was withdrawn in both groups; if needed, the inhaler was tapered as follows: up to 8 per day during month 4, up to 6 per day during month 5, and up to 3 per day during month 6. No treatment was administered after the end of month 6. Subjects were then followed up for an additional 6 months.

Any concomitant medication was registered at baseline. Any other therapy considered necessary was given at the discretion of the investigator, with all such treatment recorded in the case report form.

Continued on next page

tine during inhalation. In double-blind, placebo-controlled trials, abstinence rates were significantly higher for the groups that received a nicotine 10-mg inhaler than the placebo inhaler groups.^{14,15}

However, the different nicotine delivery systems have rather modest overall long-term success rates, ranging from 17% to 35%.^{5,13-15} Interestingly, a dose-response success rate has been reported with the nicotine gum and the nicotine patch,¹⁶⁻²⁰ and combinations of 2 delivery systems appear to improve cessation outcome.²¹⁻²⁴ We therefore investigated the effect of combining the nicotine 10-mg inhaler, a self-dosing system, with the transdermal nicotine 16-hour patch, a fixed-dose system deliv-

ering 15 mg of nicotine per 16 hours, on the long-term successful quit rate. This treatment combination offers an additional advantage in that the nicotine inhaler replaces some of the oral, handling, and sensory reinforcements of smoking behavior.

The objectives of this study were to investigate whether short-term (6-week) addition of a nicotine patch to nicotine inhaler treatment improves early smoking cessation rates, and whether this treatment combination improves the likelihood of abstinence at 6 and 12 months. The study also investigated whether use of the nicotine inhaler increased after switching from active to placebo patch or after discontinuation of patch treatment. Any

ASSESSMENTS

At baseline, the day before quit day, patient characteristics and vital signs were assessed. Subjects were weighed (minus shoes and excess clothes) on scales that were used throughout the study. A smoking history was obtained and the carbon monoxide content of expired air was measured by asking subjects to inhale deeply, hold for 15 seconds, and exhale slowly and forcefully through a monitor (EC50 Bedfont; Technical Instruments, Sittingbourne, England). Cotinine level was determined by collecting whole blood from an arm vein into venoject tubes containing heparin sodium. Questionnaires were used to evaluate the psychological status (General Health Questionnaire,²⁵ Perceived Stress Scale Questionnaire²⁶), smoking assessment and reasons for stopping smoking, nicotine dependence (Fagerström Test for Nicotine Dependence),²⁷ and socioeconomic status. Medical history was obtained by means of a standard questionnaire, and respiratory symptoms were assessed with the European Coal and Steel Community questionnaire.²⁸

Pulmonary function tests were measured according to the American Thoracic Society recommended standards.²⁹ Spirometry was performed with an electronic spirometer (Minato, Autospiro AS-500; Société Mediprom, Paris, France) by asking the subjects to exhale forcefully after a maximal inspiratory maneuver. At least 3 volume-time and flow-volume curves were obtained, from which the following measures were calculated: forced vital capacity, forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF), and maximal expiratory flow at 50% (V̇max₅₀) and 25% (V̇max₂₅) of the forced vital capacity. As our purpose was to evaluate the relationship between baseline and subsequent changes in lung function with time, absolute values were used.

During treatment and follow-up, weight was measured, smoking status and expired carbon monoxide were assessed, and blood cotinine was measured. Craving and withdrawal symptoms listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*³⁰ (anxiety, difficulty in concentration, restlessness, headache, drowsiness, hunger, depression, and sleep disturbances) were measured and all adverse events recorded. Pulmonary measures (symptoms and function) were assessed at baseline and at 12 months.

MEASURES OF OUTCOME

The primary efficacy measure was the 3-month cessation rate. Other primary outcome variables were as follows:

(1) Rate of continuous abstinence at all time points, defined as self-reported nonsmoking between week 2 and month 12 and an expired carbon monoxide level less than 10 ppm³¹ at each follow-up visit, was determined. Subjects who did not attend the follow-up visits at week 2 or later (despite a request) or who did not satisfy the above definition of abstinence were classified as relapsing subjects. Relapse was categorized as a failure in the primary evaluation, but it did not necessitate withdrawal if the subject was willing to continue and was considered competent to succeed by the investigator. Subjects unavailable for follow-up were assumed to be smokers. (2) Nicotine inhaler use was evaluated with respect to possible development of tolerance to nicotine when the nicotine patch was switched to placebo patch at 6 weeks in group 1 and at 12 weeks when the placebo patch was withdrawn from both treatment groups. (3) Nicotine substitution was calculated from the geometric mean of whole-blood cotinine measurements performed at baseline and at each follow-up visit. (4) Longitudinal changes in respiratory symptoms and pulmonary function measures were evaluated. (5) The incidence of withdrawal symptoms, adverse events, and changes in body weight was determined.

STATISTICAL METHODS

The study was designed to detect (80% power; 2-tailed test for $P < .05$) at least a 15% difference between treatment groups at 3 months, with observation of abstinence rates up to 1 year. To achieve a projected success rate of 55% for group 1 (nicotine inhaler plus nicotine patch) and 40% for group 2 (nicotine inhaler plus placebo patch), 175 subjects per group were needed. Therefore, to allow for withdrawals and protocol violations, 200 subjects were included in each group.

Data were analyzed on an intent-to-treat basis (ie, all subjects who entered the study and received medication, irrespective of medication use or outcome). Intergroup differences in intent-to-treat abstinence rates at all time points were calculated by the χ^2 test (or Fisher exact test if necessary). The proportions of participants remaining abstinent over time were calculated by comparing the relapse with the smoking curves of the 2 groups by means of the log rank test. Continuous variables were compared between groups by parametric t tests whenever possible, and the Mann-Whitney rank sum test was used for data that were nonnormally distributed.

side effects and the influence of the combination therapy on the respiratory health status of participants were also measured.

RESULTS

PARTICIPANTS

Baseline patient demographic and smoking characteristics are shown in **Table 2**. There were no significant differences between the 2 groups except for a greater number of cigarettes per day in group 1. Reasons for wanting to quit smoking were similar in both groups, with con-

cerns about future health being the most common reason (**Table 3**).

ABSTINENCE RATES

Intent-to-treat rates of continuous abstinence from smoking at 4 time points are shown in **Table 4**. Abstinence rates were consistently higher in group 1 than group 2 throughout the study, but the differences were only statistically significant up to week 12. Nevertheless, analysis of the data in terms of the 1-year survival, with the proportion of participants completely abstinent from smoking as the survival variable, showed a significant as-

Table 1. Participants in Each Group at Each Time Point up to 1 Year

Time Point	Treatment, No.		Total, No.
	Group 1 (Active Patch)	Group 2 (Placebo Patch)	
Baseline	200	200	400
Week 1	190	186	376
Week 2	182	170	352
Week 6	155	142	297
Week 12	121	100	221
Month 6	67	66	133
Month 12	52	45	97

Table 2. Baseline Patient Characteristics*

Characteristic	Group 1 (n = 200)	Group 2 (n = 200)
Age, y	37.1 (8.1)	37.4 (8.8)
Sex, No. M/F	99:101	97:103
Weight, kg		
Men	77.6 (11.4)	77.8 (13.4)
Women	61.8 (12.0)	64.8 (14.8)
Height, cm		
Men	174.9 (7.2)	175.7 (7.6)
Women	163.2 (5.8)	162.5 (5.7)
Cigarettes smoked per day	26.1 (11.0)	23.5 (8.6)†
Carbon dioxide, ppm	30.5 (11.7)	29.1 (10.8)
Cigarette nicotine content, mg	1.04 (0.28)	1.01 (0.34)
Nicotine dependence, FTND score	6.28 (1.85)	6.14 (1.95)
Years of regular smoking	20.7 (8.0)	20.4 (7.8)
Previous quit attempts, No.	2.8 (2.2)	3.1 (2.8)

*FTND indicates Fagerström Test for Nicotine Dependence. Values are mean (SD) unless otherwise indicated.

†P = .009, t test.

sociation between abstinence and treatment with nicotine inhaler plus nicotine patch (log rank test; $\chi^2=4.11$; $P=.04$) (Figure).

NICOTINE SUBSTITUTION

Nicotine substitution was measured by comparing baseline cotinine levels with those observed during treatment and follow-up. In completely abstinent subjects, mean nicotine substitution during the first 6 weeks was significantly greater in group 1 than group 2 (Table 5), but this significance was not maintained at week 12.

TREATMENT USE

In completely abstinent subjects, the mean (\pm SD) number of patches used per day was 0.94 ± 0.19 in group 1 and 0.93 ± 0.16 in group 2 from quit day to week 6, representing 57.0% and 49.5% daily users, respectively ($P=.27$, χ^2 test), and 0.84 ± 0.29 in group 1 and 0.84 ± 0.30 in group 2 from weeks 6 to 12, representing 31.0% and 35.5% daily users, respectively ($P=.57$, χ^2 test). The mean number of inhaler cartridges used per day was 4.41 ± 2.53 in group 1 and 4.60 ± 2.33 in group 2 from quit day to week 6, representing 62.8% and 69.5% daily users, re-

Table 3. Subjects' Reasons for Stopping Smoking*

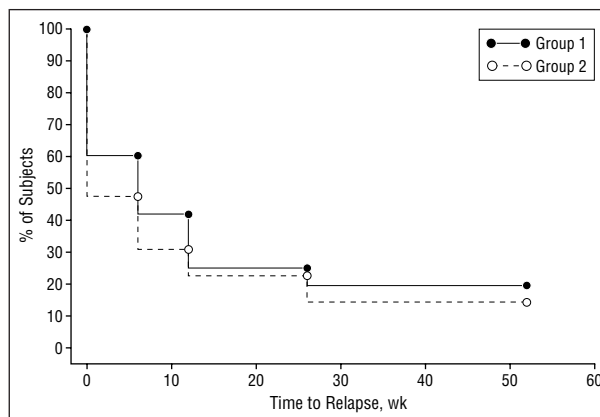
Reason	Group 1 (n = 200)	Group 2 (n = 200)
Future health concerns (self)	3.77 (0.59)	3.77 (0.59)
Present health concerns (self)	3.72 (0.63)	3.72 (0.65)
Health of others, environmental smoke	2.87 (1.10)	2.89 (1.10)
Feel smoking is out of control	2.81 (1.17)	2.85 (1.16)
Expense/cost of smoking	2.43 (1.08)	2.31 (1.13)
Peer pressure to quit	2.44 (1.19)	2.48 (1.26)

*Rated on a scale from 1 (not important) to 4 (very important). Values are mean (SD).

Table 4. Number of Participants Completely Abstinent From Smoking From Week 2 up to 12 Months

Time Point	No. (%)		P*
	Group 1 (n = 200)	Group 2 (n = 200)	
Week 6	121 (60.5)	95 (47.5)	.009
Week 12	84 (42.0)	62 (31.0)	.02
Month 6	50 (25.0)	45 (22.5)	.56
Month 12	39 (19.5)	28 (14.0)	.14

*By χ^2 test.



Time to relapse in subjects completely abstinent from week 2 to year 1. See the "Study Design and Medication" subsection of the "Subjects and Methods" section for description of treatment sequences. Log rank test, $\chi^2=4.11$, $P=.04$; Wilcoxon test, $\chi^2=6.03$, $P=.01$.

Table 5. Mean Nicotine Substitution (vs Baseline) in Completely Abstinent Subjects at Weeks 6 and 12

Time Point	Group 1*	Group 2*	P†
Week 6	60.1 (43.6-74.8)	24.6 (19.9-44.9)	<.001
Week 12	31.6 (16.9-60.0)	27.2 (16.4-67.1)	.70

*Values are percentages (95% confidence intervals).

†Wilcoxon rank sum test.

spectively ($P=.31$, χ^2 test), and 3.75 ± 2.65 in group 1 and 4.32 ± 2.50 in group 2 from weeks 6 to 12, representing 53.6% and 66.1% daily users, respectively ($P=.13$, χ^2 test); there was no increase in inhaler use after 6 weeks in group

Table 6. Incidence of Respiratory Symptoms at Baseline and at Trial End in Abstinent Subjects (Slips Allowed)

Respiratory Symptom	No. (%)					
	Group 1 (n = 46)			Group 2 (n = 34)		
	Baseline	12 mo	P*	Baseline	12 mo	P*
Cough, morning	14 (30)	0 (0)	<.001	9 (15)	0 (0)	.05
Phlegm, morning	9 (20)	0 (0)	.002	4 (12)	0 (0)	.11
Wheezing	16 (35)	2 (4)	<.001	10 (29)	3 (9)	.06
Shortness of breath	24 (52)	7 (15)	<.001	20 (59)	8 (24)	.006

*Fisher exact test.

1 when the nicotine patch was replaced with placebo. There was no increase in inhaler use in either group at 12 weeks when the placebo patch was withdrawn.

WITHDRAWAL SYMPTOMS AND ADVERSE EVENTS

Subjects in group 2 reported significantly more intense withdrawal symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, at week 1 ($P < .001$) and craving symptoms at week 6 ($P = .04$) than those in group 1. Adverse events were rare and tolerable. The most common adverse event associated with the inhaler was throat irritation, which was reported by 1 subject (0.5%) in group 1 and 2 subjects (1%) in group 2; this was transient and disappeared during treatment. The main adverse event with the patch was itching, which was reported by 14 subjects (7%) in group 1 and 4 subjects (2%) in group 2 ($P = .02$); this was also transient and disappeared after the first week. Two subjects experienced a serious adverse event, but in both the event was considered unrelated to treatment (liver cancer in group 1 and peptic ulcer in group 2). Study treatment was discontinued in the patient with liver cancer but not in the subject with peptic ulcer.

By week 2, subjects in group 1 had gained an average of 0.49 ± 1.39 kg, compared with 0.99 ± 1.02 kg in group 2 ($P = .01$). After 12 months, mean body weight gains in groups 1 and 2 were 4.22 ± 3.96 kg and 5.06 ± 2.70 kg, respectively ($P = .14$).

One year after cessation, the number of subjects complaining of respiratory symptoms fell significantly in both treatment groups (Table 6). This was particularly true of morning cough and phlegm, which disappeared altogether in abstinent subjects. Mean baseline and 1-year pulmonary function measures are shown in Table 7. One year after cessation, results showed a trend toward slightly improved values for all measures, but only the difference between baseline and 1-year peak expiratory flow reached significance.

COMMENT

To our knowledge, this is the first double-blind, placebo-controlled study to examine the efficacy and tolerability of a combination of the nicotine inhaler and nicotine patch. The active inhaler was used in both groups for 3 months, followed by a tapering period of 3

Table 7. Pulmonary Function Tests at Baseline and at 12 Months in Completely Abstinent Subjects, Irrespective of Treatment*

Variable	Baseline	12 mo	P†
FEV ₁ , L	3.35 (0.63)	3.39 (0.63)	.26
FVC, L	4.31 (0.83)	4.33 (0.82)	.50
FEV ₁ /FVC, %	77.75	78.07	.44
PEF, L/s	7.41 (1.87)	8.42 (1.70)	<.001
Vmax ₅₀ , L/s	3.86 (1.08)	3.94 (1.22)	.34
Vmax ₂₅ , L/s	1.47 (0.53)	1.47 (0.54)	.99

*Group 1, n = 39; group 2, n = 28; total, n = 67. Values are mean (SD) unless otherwise indicated. FEV₁ indicates forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; Vmax₅₀, maximal expiratory flow at 50% of the FVC; and Vmax₂₅, maximal expiratory flow at 25% of the FVC.

†t test.

months and a 6-month follow-up with no medication. The nicotine patch was used for 6 weeks in one group followed by 6 weeks of placebo patch treatment. The other group used placebo patch from the beginning up to 12 weeks. The results show that, from 2 weeks after stopping smoking, the combination treatment was significantly more effective at promoting complete abstinence than using a nicotine inhaler plus placebo patch; log rank test analysis showed a significant association between abstinence and the combination treatment (Figure).

The higher abstinence rates in group 1 up to 1 year can probably be explained by higher levels of nicotine substitution during the first 6 weeks.¹⁶⁻¹⁹ When Sachs and colleagues¹⁸ prospectively assigned smokers to receive sufficient nicotine to attain either 0%, 50%, or 100% cotinine replacement with nicotine patch therapy, in relation to their cotinine levels during baseline cigarette smoking, they found that higher cotinine replacement was associated with higher smoking cessation rates. Our study design allowed participants to self-titrate their plasma nicotine levels by using the nicotine inhaler ad libitum in addition to their patch, a fixed-dose system that yields steady nicotine levels. Subjects could therefore increase their nicotine levels during the day, which is not possible when using the patch alone.

Despite the recommendation to use at least 6 inhaler cartridges per day, subjects in group 2 (placebo patch) used only 5 cartridges per day from quit day to week 6 and so did not reach the same level of nicotine substitution as subjects in group 1, who also obtained nicotine from the patch. This finding is consistent with the idea that the level of nicotine substitution might not be the only factor governing quit rates. In a double-blind, randomized trial, Paoletti and colleagues³² found that, for a similar degree of substitution (57%), the continuous abstinence rate of smokers with high baseline plasma cotinine levels was lower than that of smokers with low baseline cotinine levels. Although our cotinine measurements were carried out in whole blood—thus preventing direct comparisons with the absolute plasma cotinine levels of the above study—they were similar in the 2 groups and cannot, therefore, explain the differences in abstinence rates we observed.

However, the possibility that the effort of obtaining more nicotine (eg, use of a greater number of in-

haler cartridges, spending more time inhaling) for subjects in group 2 outweighed the need for high substitution levels cannot be entirely ruled out.

Our cessation rates could have been influenced by the combination therapy itself. Blondal and colleagues²⁴ reported that a combination of a nicotine patch plus nicotine spray was more effective than a nicotine patch plus placebo spray. They noted that, apart from higher nicotine substitution levels, their results could have been influenced by the opportunity the spray offered the smokers to respond quickly to their needs. However, in the Blondal et al study, one group received active spray and the other a placebo spray, whereas in our study both groups received active nicotine inhalers. Thus, the beneficial effects of the nicotine inhaler, in terms of both nicotine replacement and oral and handling reinforcement, were available to subjects in both groups. Incidentally, the use of a similar number of inhalers is consistent with the theory that the ritual therapy was equally important for our 2 groups.

In addition to the nicotine nasal spray plus nicotine patch study,²⁴ 2 other studies, both of which used nicotine chewing gum plus nicotine patch, have evaluated the efficacy of combination NRT for smoking cessation.^{22,23} Both studies demonstrated that subjects who used combination NRT achieved higher abstinence rates than those who used 1 NRT system alone. An early NRT combination study²¹ using nicotine patch plus nicotine chewing gum also showed superior relief of withdrawal symptoms compared with NRT monotherapy. In our study, the placebo component was the fixed-dose rather than the self-dosing delivery system.^{23,24} With this difference in mind, our short-term (up to 3 months) cessation rates are higher and our long-term (6 and 12 months) rates are similar to or slightly lower than those previously reported.

The present study corroborates previous reports on the efficacy of the nicotine inhaler. Indeed, the cessation rates of our group 2 (nicotine inhaler plus placebo patch) are superior to the rates observed in previous studies of the nicotine inhaler vs placebo at similar time points.^{14,15} However, these results should be interpreted with caution because of the different countries in which the studies were conducted as well as possible differences in the settings and study designs.

Our study also confirmed that combination NRT was superior to single NRT treatment in terms of nicotine substitution, and confirmed the substitution of greater than 50% of smoking levels previously reported with combination NRT.²²⁻²⁴ Pooling the results from this study and other combination studies²²⁻²⁴ (n=1236) gives an odds ratio for cessation at 12 months of 1.7 (95% confidence interval, 1.3-2.3) compared with using single NRT, which represents a further increase of the same magnitude as that achieved with any single NRT compared with placebo treatment.

At the 12-month follow-up, our abstinent subjects displayed an impressive improvement in respiratory symptoms; wheezing and shortness of breath were significantly reduced, and cough and phlegm had completely disappeared (Table 6). The latter finding is in keeping with the fact that cigarette smoking is the most impor-

tant factor associated with the occurrence of hypersecretion,³³ the prevalence of which increases with increasing cigarette consumption.³⁴

A trend toward improvement in pulmonary function measures was observed in completely abstinent subjects pooled from groups 1 and 2 (Table 7). This is an important finding, given that cigarette smoking accelerates the rate of decline in pulmonary function beyond that usually related to age.³⁵ However, rather than decreasing with age, the forced expiratory volume in 1 second of our abstinent subjects increased by an average of 40 mL. Although not statistically significant, this improvement is clinically relevant and is far superior to that observed (approximately 15 mL/y) in a recent 6-year follow-up of a large cohort of middle-aged men.³⁶ In summary, the pulmonary findings in our study confirm the beneficial respiratory effects of smoking cessation and that the slowing down of the decline in forced expiratory volume in 1 second appears to be relatively rapid in those who quit smoking.

In conclusion, this study demonstrates that the combination of the nicotine patch (delivering 15 mg of nicotine per 16 hours) and the nicotine inhaler (containing 10 mg of nicotine but delivering approximately 4 mg if used optimally) is a more effective method of stopping smoking than using the nicotine inhaler alone in a low-intervention context. This study supports the theory that the administration of nicotine via different formulations can improve short- and long-term abstinence rates. Such combinations may be particularly appropriate for highly dependent smokers with a strong behavioral component to their smoking pattern.

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