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.

Arch Intern Med. 2000;160:3128-3134
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
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% (V·max50) and 25% (V·max25) 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 Edition30 (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 13% difference between treatment groups at 3 months, with observation of abstinence rates up to 1 year. To achieve a projected success rate of 33% 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 χ² 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.

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-
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 (± 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 (\( P = .27, \chi^2 \)-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 (\( P = .57, \chi^2 \)-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, respectively (\( P = .31, \chi^2 \)-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 (\( P = .13, \chi^2 \)-test); there was no increase in inhaler use after 6 weeks in group 1.

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

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

**Table 2. Baseline Patient Characteristics**

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

*FTND indicates Fagerström Test for Nicotine Dependence. Values are mean (SD) unless otherwise indicated. \( \dagger P = .009 \), t-test.

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**Table 3. Subjects’ Reasons for Stopping Smoking**

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

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

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

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Group 1 (n = 200)</th>
<th>Group 2 (n = 200)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>121 (60.5)</td>
<td>95 (47.5)</td>
<td>.009</td>
</tr>
<tr>
<td>Week 12</td>
<td>84 (42.0)</td>
<td>62 (31.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Month 6</td>
<td>50 (25.0)</td>
<td>45 (22.5)</td>
<td>.56</td>
</tr>
<tr>
<td>Month 12</td>
<td>39 (19.5)</td>
<td>28 (14.0)</td>
<td>.14</td>
</tr>
</tbody>
</table>

*By \( \chi^2 \)-test.

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

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Group 1 (n = 200)</th>
<th>Group 2 (n = 200)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>60.1 (43.6-74.8)</td>
<td>24.6 (19.9-44.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Week 12</td>
<td>31.6 (16.9-60.0)</td>
<td>27.2 (16.4-67.1)</td>
<td>.70</td>
</tr>
</tbody>
</table>

*Values are percentages (95% confidence intervals). \( \dagger \) Wilcoxon rank sum test.

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*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, \( \chi^2 = 6.03, P = .01 \).*
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 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. When Sachs and colleagues 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, Paolletti and colleagues 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-

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

<table>
<thead>
<tr>
<th>Respiratory Symptom</th>
<th>Group 1 (n = 46)</th>
<th>Group 2 (n = 34)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12 mo</td>
<td>Baseline 12 mo</td>
<td></td>
</tr>
<tr>
<td>Cough, morning</td>
<td>14 (30) 0 (0)</td>
<td>&lt; .001 9 (15) 0 (0)</td>
<td>.05</td>
</tr>
<tr>
<td>Phlegm, morning</td>
<td>9 (20) 0 (0)</td>
<td>.002 4 (12) 0 (0)</td>
<td>.11</td>
</tr>
<tr>
<td>Wheezing</td>
<td>16 (35) 2 (4)</td>
<td>&lt; .001 10 (29) 3 (9)</td>
<td>.06</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>24 (52) 7 (15)</td>
<td>&lt; .001 20 (59) 8 (24)</td>
<td>.006</td>
</tr>
</tbody>
</table>

*Fisher exact test.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>12 mo</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, L</td>
<td>3.35 (0.63)</td>
<td>3.39 (0.63)</td>
<td>.26</td>
</tr>
<tr>
<td>FVC, L</td>
<td>4.31 (0.83)</td>
<td>4.33 (0.82)</td>
<td>.50</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>77.75</td>
<td>78.07</td>
<td>.44</td>
</tr>
<tr>
<td>PEF, L/s</td>
<td>7.41 (1.87)</td>
<td>8.42 (1.70)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Vmax50, L/s</td>
<td>3.86 (1.08)</td>
<td>3.94 (1.22)</td>
<td>.34</td>
</tr>
<tr>
<td>Vmax25, L/s</td>
<td>1.47 (0.53)</td>
<td>1.47 (0.54)</td>
<td>.99</td>
</tr>
</tbody>
</table>

*Group 1, n = 38; 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.
haler cartridges, spending more time inhaling) for sub-
jects 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 nic-
toine spray was more effective than a nicotine patch plus
placebo spray. They noted that, apart from higher nico-
toine substitution levels, their results could have been
influenced by the opportunity the spray offered the smok-
ers 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 ben-
eficial effects of the nicotine inhaler, in terms of both nico-
toine 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 nico-
toine patch study,24 2 other studies, both of which used
nicotine chewing gum plus nicotine patch, have evalu-
ated the efficacy of combination NRT for smoking ces-
sation.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 study,21 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 With this dif-
ference in mind, our short-term (up to 3 months) ces-
sation 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 cessa-
tion rates of our group 2 (nicotine inhaler plus placebo
patch) are superior to the rates observed in previous stud-
ies 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 differ-
ences in the settings and study designs.

Our study also confirmed that combination NRT was
superior to single NRT treatment in terms of nicotine sub-
stitution, and confirmed the substitution of greater than
50% of smoking levels previously reported with combi-
nation 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 pla-
cebo treatment.

At the 12-month follow-up, our abstinent subjects
displayed an impressive improvement in respiratory symp-
toms; wheezing and shortness of breath were signifi-
cantly 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 hyperse-
cretion,23 the prevalence of which increases with increas-
ing cigarette consumption.24

A trend toward improvement in pulmonary func-
tion measures was observed in completely abstinent sub-
jects pooled from groups 1 and 2 (Table 7). This is an
important finding, given that cigarette smoking accel-
erates the rate of decline in pulmonary function beyond
that usually related to age.35 However, rather than de-
creasing with age, the forced expiratory volume in 1 sec-
don of our abstinent subjects increased by an average of
40 mL. Although not statistically significant, this im-
provement is clinically relevant and is far superior to that
observed (approximately 15 mL/min) in a recent 6-year fol-
low-up of a large cohort of middle-aged men.36 In sum-
mary, 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 vol-
ume in 1 second appears to be relatively rapid in those
who quit smoking.

In conclusion, this study demonstrates that the com-
bination of the nicotine patch (delivering 15 mg of nico-
tine 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 formul-
aions can improve short- and long-term abstinence rates.
Such combinations may be particularly appropriate for
highly dependent smokers with a strong behavioral com-
ponent to their smoking pattern.

Accepted for publication January 20, 2000.

This study was supported by a grant from Pharmacia &
Upjohn Consumer Healthcare, Helsingborg, Sweden.

We are indebted to Marceau Haas, RN, and the nurs-
ing staff of the Pulmonary Service of the Centre Hospitalier
Universitaire of Nancy-Brabois for their invaluable help in
blood collection and storage; to Marie-Antoinette Hoff-
man, PharmD, from the hospital pharmacy, for dispensing
medication; and especially to Nathalie Thomas for her
archiving and secretarial assistance.

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