

Nurse-Conducted Smoking Cessation in Patients With COPD Using Nicotine Sublingual Tablets and Behavioral Support*

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Context: Few studies have examined the effect of nicotine replacement therapy (NRT) in COPD patients.

Study objective: To evaluate the efficacy of nicotine sublingual tablets and two levels of support for smoking cessation in COPD patients.

Design: Double-blind, multicenter, placebo-controlled smoking cessation trial.

Setting: Pulmonary outpatient clinics.

Patients: Three hundred seventy COPD patients who smoked a mean of 19.6 cigarettes per day (mean, 42.7 pack-years; mean FEV₁, 56% of predicted).

Interventions: Nicotine sublingual tablet or placebo for 12 weeks combined with either low support (four visits plus six telephone calls) or high support (seven visits plus five telephone calls) provided by nurses.

Measurements: Carbon monoxide-verified abstinence rates and St. George Respiratory Questionnaire (SGRQ) assessed at 6 months and 12 months.

Results: Two hundred eighty-eight of 370 patients were evaluable for the final study end points. Smoking cessation rates were statistically significantly superior with sublingual nicotine vs placebo for all measures of abstinence: 6-month point prevalence, 23% vs 10%; 12-month point prevalence, 17% vs 10%. There was no significant difference in effect between low vs high behavioral support. The SGRQ score improved significantly in abstainers vs nonabstainers; the changes in mean scores were -10.9 vs -2.9 for total score, and -28.6 vs -2.3 for symptom score, respectively.

Conclusions: This trial demonstrated the long-term efficacy of NRT for cessation for the general population of COPD smokers, regardless of daily cigarette consumption. Cessation success rates were in the same range as in healthy smokers, and abstinence improved SGRQ scores. NRT should be used to aid cessation in all smokers with COPD, regardless of disease severity and number of cigarettes smoked. (CHEST 2006; 130:334-342)

Key words: behavioral support; COPD; lung function; nicotine sublingual tablet; quality of life; smoking cessation; smoking reduction

Abbreviations: CI = confidence interval; FTND = Fagerström Test of Nicotine Dependence; NRT = nicotine replacement therapy; SGRQ = St. George Respiratory Questionnaire

Smoking cessation is the most important intervention in patients with COPD in order to stop further decline in lung function, assessed as FEV₁.^{1,2} The efficacy of nicotine replacement therapy (NRT) and bupropion for smoking cessation in healthy smokers has been investigated in numerous controlled trials but surprisingly few studies have been performed in COPD patients.³⁻⁷ One study⁸ of

bupropion in COPD patients reported lower success rates compared to healthy smokers; although a significant active vs placebo treatment effect was observed up to 6 months, this effect was lost after 1 year. The lower abstinence rate noted might reflect the fact that COPD patients are more resistant to treatment than healthy smokers.^{9,10} Regarding NRT, although efficacy in smoking cessation in healthy

smokers has been documented in > 100 trials,⁵ no well-powered randomized controlled trials have been reported in COPD patients.¹¹

As COPD patients may have more difficulty quitting, we wanted to evaluate whether more clinic visits would increase abstinence rates, as is the case in healthy smokers.³ However, the study design was

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not so intensive that it would not be practical for daily clinical use. The nicotine sublingual tablet was chosen because it can be dose titrated by the patient with *ad lib* administration and is easier to use than nicotine gum.¹²

In addition to smoking cessation, smoking reduction, *ie*, smoking fewer cigarettes daily, was also evaluated during follow-up. Although epidemiologic studies^{13,14} have shown no benefit of reduced smoking in COPD patients with regard to hospitalization and mortality, some studies^{15,16} have shown that smoking reduction might be a gateway to cessation.

The aim of this study was to evaluate the efficacy of the nicotine sublingual tablet or placebo combined with either low or high behavioral support for smoking cessation in COPD patients after 6 months and 12 months. The primary end point was smoking cessation; secondary end points were the degree of smoking reduction after 12 months and changes in quality of life measures.

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MATERIALS AND METHODS

Patients

Patients with COPD previously diagnosed by a physician were recruited from seven lung clinics using newspaper advertisements in some centers. The first patient was enrolled in February 2002, and the last patient was enrolled in June 2004. Patients enrolled were aged ≥ 18 years; were smoking one or cigarettes a day; had persistent airway obstruction with $FEV_1/FVC < 70\%$ and $FEV_1 < 90\%$ of predicted normal value; and were willing to follow the study protocol. Lung function testing was performed according to standard guidelines,^{17,18} and all values were after bronchodilation, 15 min after administration of terbutaline, 1.5 mg. Patients who had used either nicotine sublingual tablets or bupropion during the previous 7 days, or who had any disease with predicted survival < 1 year, or were unable to adhere to the protocol were excluded from the study. All participants provided informed consent, and the study protocol was approved by the Regional Ethics Committee and National Board for Drug Regulation.

Study Design

This was an investigator-initiated, double-blind, placebo-controlled trial with a 2×2 design with four treatment groups: nicotine sublingual tablet plus low support, nicotine sublingual tablet plus high support, placebo sublingual tablet plus low support, and placebo sublingual tablet plus high support (Fig 1). Patients were allocated to one of the four treatment groups using a block randomization list at each center.

Clinic Visits

In the low-support group, four visits were scheduled: at study entry, after 2 weeks, and after 6 months and 12 months, plus six telephone calls after 1, 4, 6, 9, and 12 weeks and 9 months. In the high-support group, seven visits were scheduled: at study entry, after 2, 4, 8, and 12 weeks, and 6 months and 12 months, plus five telephone calls after 1, 6, and 10 weeks, and 4.5 months and 9 months.

All visits were on an individual basis and were conducted by nurses. Each visit lasted 20 to 30 min, and each telephone call was 10 min. The total contact time was 2.5 h for the low-support groups and 4.5 h for the high-support groups. At each visit,

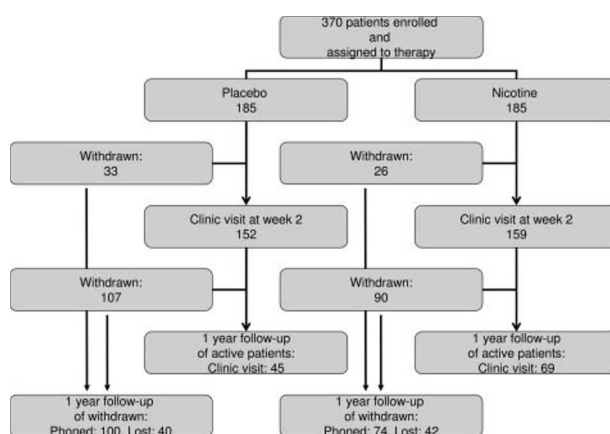


FIGURE 1. Flowchart of study.

counseling on smoking cessation was provided, and subjects were also given take-home material with tips on smoking cessation. The term *smokers lung* was used to explain COPD to subjects.

Twenty nurses with experience of smoking cessation were involved in the study. Four training meetings were held for the nurses, focusing on the importance of how to increase daily use of study medication, and to standardize the proactive counseling during both clinic visits and telephone calls. A standardized counseling guideline was printed on the reverse of the case report form, covering use of sublingual tablets, how to handle withdrawal symptoms, how to prevent relapses, and possible benefits of quitting smoking. Nine newsletters for the nurses were also produced during the study period.

NRT

Subjects were recommended to use study medication, either nicotine sublingual tablet or placebo, for 12 weeks with the possibility of continued use for up to 12 months following individual evaluation. Each nicotine sublingual tablet contains 2 mg of nicotine, and dissolves within 15 to 20 min when placed under the tongue.¹² The placebo tablets were identical in appearance to the active tablet but contained 3 µg of capsaicin and no nicotine. The recommended dose of study medication was dependent on baseline cigarette consumption: subjects who smoked ≥ 16 cigarettes per day were instructed to use 1 to 2 tablets per hour (minimum of 10 tablets and maximum of 40 tablets per day); those smoking 10 to 15 cigarettes per day were instructed to use 1 tablet per hour (6 to 30 tablets per day); and those smoking 6 to 9 cigarettes per day were instructed to use 1 tablet per hour (3 to 10 tablets per day). During each investigator meeting, the importance of adequate dosing with study medication was emphasized. The medication was free of charge.

Assessments

The main assessments were performed at entry and after 6 months and 12 months. Subjects who did not attend the 1-year visit were contacted by telephone to assess smoking status.

Expired carbon monoxide levels were measured using a carbon monoxide analyzer (Bedfont Smokerlyzer; Bedfont Scientific Limited; Rochester, Kent, UK). Any subject with an expired carbon monoxide level ≥ 10 ppm was categorized as a smoker.¹⁹ Body weight was measured at each visit with shoes and coat removed. Nicotine dependence was assessed using the Fagerström Test of Nicotine Dependence (FTND), which ranks dependence from 0 (none) to 10 (maximum).²⁰

Motivation to quit and reduce smoking were assessed on a 10-cm visual analog scale using the following questions: "How motivated are you to quit smoking completely?" and "How motivated are you to reduce your number of cigarettes now?"

The St. George Respiratory Questionnaire (SGRQ) is designed specifically to measure health-related quality of life in patients with COPD.^{21,22} The three measured aspects are disease symptoms, disease impact, and impairment of daily activities; an individual score is calculated for each of these three scales and, in addition, a total score, where 100 represents the worst case and 0 is the best possible quality of life. A reduction in the total SGRQ score of ≥ 4 is considered to represent a clinically significant improvement.^{23–25} Adverse events were monitored throughout the study by asking subjects an open-ended question at each visit.

Definition of Success

Point prevalence abstinence after 6 months and 12 months was defined as self-reported abstinence during the previous week,

verified by an exhaled carbon monoxide level < 10 ppm. *Sustained abstinence* was defined as self-reported abstinence, combined with a carbon monoxide < 10 ppm, at all visits from week 2 until month 12. Point prevalence smoking reduction included only those subjects still smoking daily at the end points and who reduced their smoking to less than seven cigarettes daily (representing a reduction of at least one cigarette per day) or reduced their daily smoking to $< 50\%$.

Sample Size and Statistical Analysis

Based on the assumption of success rates of 30% in the active study arms and 15% in the placebo arms, a total of 134 patients were needed in each arm for a power of 80% and a two-tailed significance level of 0.05. The analysis of treatment effect was calculated on an intention-to-treat basis, with subjects who withdrew regarded as failures and included in the outcome analyses. The main outcome was analyzed using logistic regression, adverse events were analyzed using Poisson regression with time on medication as exposure time, and predictors of outcome were analyzed using multinomial logistic regression. All analyses were done using statistical software (Stata Statistical Software Release 9; Stata Corporation; College Station, TX). All tests were two tailed, with a significance level of 5% considered significant.

RESULTS

Baseline Characteristics and Study Completion

A total of 370 COPD patients were enrolled in the four treatment arms (Table 1). Overall, the average age was 61.0 years and mean FEV₁ was 55.8% of predicted. In terms of COPD severity, 9% of subjects had FEV₁ $> 80\%$ of predicted, 53% had FEV₁ 50 to 80% of predicted, 30% had FEV₁ 30 to 50% of predicted, and 8% had FEV₁ $< 30\%$ of predicted. At baseline, the study population smoked a mean of 19.6 cigarettes per day (mean, 42.7 pack-years). Fewer than one tenth of those enrolled smoked < 7 cigarettes per day (7.6%) or > 30 cigarettes per day (8.1%). Three fourths of patients (71%) had previously used NRT, but only 4% had tried bupropion before. The four treatment groups were well balanced (Table 1).

At the 1-year visit, 288 patients were followed up: 114 patients attended a clinic visit, and 174 patients were contacted by telephone (Fig 1). Eighty-two patients (22%) were not available for follow-up; the most common reasons for premature withdrawal were lack of motivation to quit (31%), lack of effect from study medication (8%), side effects from study medication (8%), wanted to try another smoking cessation medication (7%), and not attending visits (22%).

Smoking Cessation

As there was no statistical interaction between treatments, *ie*, no effect modification between behavioral support and sublingual medication for all

Table 1—Baseline Characteristics of COPD Study Subjects*

| Characteristics | Placebo and Low Support | Placebo and High Support | Nicotine and Low Support | Nicotine and High Support |
|--|-------------------------|--------------------------|--------------------------|---------------------------|
| Smokers, No. | 88 | 97 | 95 | 90 |
| Male/female gender, No. | 40/48 | 46/51 | 45/50 | 46/44 |
| Age, yr | 62.5 ± 9.3 | 61.2 ± 9.4 | 59.2 ± 10.3 | 61.3 ± 9.6 |
| FEV ₁ , L | 1.57 ± 0.68 | 1.64 ± 0.60 | 1.62 ± 0.65 | 1.54 ± 0.67 |
| FEV ₁ , % of predicted normal value | 56.0 ± 19.1 | 58.2 ± 17.8 | 55.1 ± 15.4 | 53.4 ± 19.4 |
| FVC, L | 2.76 ± 1.06 | 2.75 ± 0.78 | 2.84 ± 0.99 | 2.72 ± 0.97 |
| FVC, % of predicted normal value | 73.8 ± 20.9 | 73.1 ± 16.4 | 73.4 ± 17.5 | 71.3 ± 19.2 |
| FEV ₁ /FVC, % | 56.2 ± 9.5 | 59.1 ± 10.0 | 57.0 ± 9.4 | 55.4 ± 11.3 |
| Daily cigarettes, No. | 20.2 ± 9.6 | 19.9 ± 8.8 | 20.1 ± 10.7 | 18.3 ± 10.4 |
| Pack-years | 44.9 ± 17.2 | 43.6 ± 14.7 | 40.3 ± 17.1 | 42.0 ± 19.7 |
| Carbon monoxide, ppm | 15 ± 9 | 16 ± 8 | 16 ± 9 | 16 ± 8 |
| FTND score (0–10) | 6.4 ± 1.9 | 6.4 ± 1.8 | 6.0 ± 2.1 | 5.9 ± 2.2 |
| Previous quit attempts, No. | 2.1 ± 2.3 | 3.3 ± 6.3 | 2.7 ± 3.4 | 2.2 ± 2.3 |
| Duration of longest quit attempt, d | 161 ± 512 | 125 ± 341 | 183 ± 497 | 122 ± 232 |
| Previous use of NRT, % | 66 ± 48 | 75 ± 43 | 72 ± 45 | 71 ± 46 |
| Motivation to quit smoking (scale of 0–10) | 8.2 ± 2.1 | 8.1 ± 2.5 | 8.4 ± 2.1 | 7.9 ± 2.7 |
| Motivation to reduce smoking (scale of 0–10) | 8.0 ± 2.3 | 8.5 ± 2.0 | 8.4 ± 2.3 | 8.1 ± 2.4 |
| SGRQ symptoms | 48.8 ± 21.6 | 54.8 ± 22.5 | 50.7 ± 22.0 | 52.9 ± 21.4 |
| SGRQ impact | 29.4 ± 19.2 | 29.0 ± 17.7 | 28.0 ± 17.4 | 30.4 ± 18.8 |
| SGRQ activity | 47.7 ± 23.8 | 44.8 ± 23.1 | 41.4 ± 24.7 | 48.8 ± 24.4 |
| SGRQ total | 38.1 ± 19.1 | 38.1 ± 18.0 | 35.8 ± 18.2 | 39.9 ± 19.2 |

*Data are presented as mean ± SD unless otherwise indicated.

outcome measures (likelihood ratio test, $p = 0.20$, $p = 0.18$, and $p = 0.74$ for point prevalence abstinence at 6 months and 12 months, and sustained abstinence, respectively), only the main effect of nicotine medication and behavioral support is reported.

All abstinence measures (point prevalence abstinence at 6 months and 12 months, and sustained abstinence from week 2 to 12 months) were significantly higher with the sublingual nicotine tablet than

with placebo throughout the study (Table 2). Six-month point prevalence abstinence and sustained abstinence were more than doubled with the active tablet, and the active treatment effect was almost double for 12-month point prevalence abstinence.

The effect of high vs low behavioral support was statistically insignificant for all abstinence outcome measures (Table 2). However, although not statistically significant, the estimate of the effect of behavioral support was consistently higher in the placebo

Table 2—Point Prevalence and Sustained Abstinence Rates for All Four Treatment Groups ($n = 370$)*

| Treatment Groups | Low Support (n = 183) | High Support (n = 187) | Total (n = 370) | Odds Ratio (95% CI)† |
|--------------------------------------|--------------------------|---------------------------|--------------------|-------------------------|
| Six-month point prevalence | | | | |
| Placebo (n = 185) | 6 (5/88) | 13 (13/97) | 10 (18/185) | 3.46 (1.58–5.2) |
| Nicotine tablet (n = 185) | 22 (21/95) | 24 (22/90) | 23 (43/185) | |
| Total | 14 (26/183) | 19 (35/187) | | |
| Odds ratio (95% CI)‡ | 1.46 (0.83–2.57) | | | |
| Twelve-month point prevalence | | | | |
| Placebo (n = 185) | 6 (5/88) | 13 (13/97) | 10 (18/185) | 1.97 (1.06–3.67) |
| Nicotine tablet (n = 185) | 17 (16/95) | 18 (16/90) | 17 (32/185) | |
| Total | 11 (21/183) | 16 (29/187) | | |
| Odds ratio (95% CI)‡ | 1.46 (0.79–2.68) | | | |
| Sustained abstinence (wk 2 to 12 mo) | | | | |
| Placebo (n = 185) | 5 (4/88) | 6 (6/97) | 5 (10/185) | 2.88 (1.34–6.16) |
| Nicotine tablet (n = 185) | 14 (13/95) | 14 (13/90) | 14 (26/185) | |
| Total | 9 (17/183) | 10 (19/183) | | |
| Odds ratio (95% CI)‡ | 1.15 (0.57–2.31) | | | |

*Data are presented as % (No./total).

†Nicotine sublingual tablets vs placebo.

‡Low support vs high support.

group. When the effect of behavioral support was estimated using the placebo-treated group only, the effect was borderline significant ($p < 0.10$) for the point prevalence abstinence outcome measures (data not shown).

Point Prevalence Smoking Reduction

Only those subjects still smoking daily at follow-up were considered evaluable for the smoking reduction end point. There was no statistical interaction between treatments, *ie*, no effect modification between behavioral support and study medication (likelihood ratio test, $p = 0.74$ and $p = 0.85$ for point prevalence smoking reduction at 6 months and 12 months, respectively). There was no obvious effect of either nicotine medication or behavioral support. After 12 months, 13% of patients had reduced their smoking (Table 3). Among all reducers, mean daily cigarette consumption declined from 18/d at baseline to 4/d at both 6 months and 12 months. Expired carbon monoxide declined from 15 ppm at baseline to 10 ppm at 6 months and to 2 ppm at 12 months.

Use of NRT

The mean daily number of tablets used during week 1 was 6.5 in the placebo plus low-support group, 8.8 in the placebo plus high-support group, 8.7 in the nicotine tablet plus low-support group, and 7.0 in the nicotine tablet plus high-support group. At week 8, the corresponding numbers of tablets per day were 7.3, 9.6, 7.2, and 8.6, respectively. The gradual self reduction in dose noted (-0.18 tablets per day per week) did not differ between the four treatment groups.

Adverse Events

A total of 671 adverse events were reported throughout the study and were coded into 142

categories. The most common adverse events, which comprised 50% of all events, were itching in the mouth (9.4%), flu or cold (4.6%), cough (4.5%), exacerbation of COPD (4.2%), unpleasant taste (3.7%), pneumonia (3.7%), diarrhea (3.7%), dry mouth (3.0%), dyspepsia (2.7%), nausea (2.7%), dizziness (2.5%), breathlessness (2.5%), and headache (2.4%). Twenty-two patients withdrew because of adverse events.

The adverse event incidence rates (number of events by "patient \times treatment period") were similar in the high and low behavioral support groups and in the nicotine- and placebo-treated groups: incidence rate ratio (high vs low), 0.89 (95% confidence interval [CI], 0.76 to 1.05), and IRR (active vs placebo), 1.08 (95% CI, 0.92 to 1.27). Fourteen patients died during the 12-month study, 6 in the nicotine group and 8 in the placebo group; none of these deaths were related to study treatment.

Predictors of Outcome

Multinomial logistic regression was used to analyze whether the two outcomes of smoking reduction and sustained abstinence were associated with different groups of predictors. Table 4 shows the odds ratios and associated p values and 95% CIs for factors predictive of either of two outcomes, with the failures as the reference group. A number of other factors (age, gender, FEV₁ percentage of predicted, cigarettes per day, nicotine contents, pack-years, previous quit attempts, FTND, and SGRQ activity and total scores) were also included in an initial regression model but were not found to be statistically significant associated with neither of the two outcomes.

Smoking abstinence was related to nicotine sublingual treatment, high body mass, low carbon monoxide, duration of previous quit attempt, low moti-

Table 3—Point Prevalence Smoking Reduction (Daily Smokers of Less Than Seven Cigarettes per Day and Who Reduced by at Least One Cigarette per Day vs Entry and/or Reduction to $< 50\%$ vs Entry) Rate for All Four Groups at 6 Months and 12 Months*

| Treatment Groups | Low Support (n = 183) | High Support (n = 187) | Total (n = 370), % | Odds Ratio (95% CI)† |
|---|--------------------------|---------------------------|-----------------------|-------------------------|
| Six-month point prevalence smoking reduction | | | | |
| Placebo (n = 185) | 14.8 (13/88) | 15.5 (15/97) | 15.1 | 1.50 (0.88–2.55) |
| Nicotine tablet (n = 185) | 22.1 (21/95) | 20.0 (18/90) | 21.1 | |
| Total, % | 18.6 | 17.6 | 18.1 | |
| Odds ratio (95% CI)‡ | 0.95 (0.56–1.62) | | | |
| Twelve-month point prevalence smoking reduction | | | | |
| Placebo (n = 185) | 11.4 (10/88) | 14.4 (14/97) | 13.0 | 0.96 (0.52–1.78) |
| Nicotine tablet (n = 185) | 11.6 (11/95) | 13.3 (12/90) | 12.4 | |
| Total, % | 11.5 | 13.9 | 12.7 | |
| Odds ratio | 1.24 (0.67–2.30) | | | |

*Data are presented as % (No./total) unless otherwise indicated.

†Nicotine sublingual tablets vs placebo.

‡High support vs low support.

Table 4—Predictors of Smoking Reduction and Abstinence in Multinomial Logistic Regression Analysis With Failures as Reference Group

| Variables | Odds | | 95% CI |
|--|-------|---------|-----------|
| | Ratio | p Value | |
| Reducers compared to failures | | | |
| Sublingual nicotine tablets vs placebo | 1.04 | 0.911 | 0.54–1.98 |
| High support vs low support | 1.23 | 0.540 | 0.64–2.36 |
| Body mass index | 0.93 | 0.057 | 0.86–1.00 |
| Carbon monoxide | 0.98 | 0.307 | 0.94–1.02 |
| Duration of previous quit attempt | 1.00 | 0.735 | 1.00–1.00 |
| Motivation to reduce | 1.06 | 0.589 | 0.86–1.30 |
| Motivation to quit | 1.00 | 0.961 | 0.84–1.18 |
| SGRQ symptoms | 1.02 | 0.035 | 1.00–1.04 |
| SGRQ impact | 0.98 | 0.126 | 0.96–1.01 |
| Abstainers compared to failures | | | |
| Sublingual nicotine tablets vs placebo | 3.68 | 0.002 | 1.61–8.41 |
| High support vs low support | 1.39 | 0.403 | 0.64–3.00 |
| Body mass index | 1.08 | 0.067 | 0.99–1.17 |
| Carbon monoxide | 0.89 | 0.000 | 0.84–0.95 |
| Duration of previous quit attempt | 1.00 | 0.071 | 1.00–1.00 |
| Motivation to reduce | 0.78 | 0.006 | 0.66–0.93 |
| Motivation to quit | 1.21 | 0.072 | 0.98–1.49 |
| SGRQ symptoms | 1.01 | 0.436 | 0.99–1.03 |
| SGRQ impact | 0.97 | 0.051 | 0.95–1.00 |

vation to reduce and high motivation to quit, and low SGRQ impact score (*ie*, low impact). Smoking reduction was associated with low body mass and high SGRQ symptom score.

Changes in SGRQ Scores, FEV₁, and Body Weight

The following analyses of outcome groups are based exclusively on the 113 patients who completed the trial per protocol, with 1-year follow-up. Another patient who attended the 1-year visit was excluded due to missing data. Of these 113 patients, 36 were successful sustained abstainers, 46 were reducers, and 31 were failures (continued smoking with no reduction).

SGRQ Scores at 1 Year

Reducers and sustained abstainers had both clinically and statistically significant improvements in all SGRQ score types and, with the exception of the activity score, improvements were greater in sus-

tained abstainers than in reducers (Table 5). When plotted against time, the improvements were similar for reducers and sustained abstainers until week 26, after which reducers leveled off, whereas the sustained abstainers continued to improve, albeit at a much lower rate, until week 52 when follow-up ended (data not shown). For both reducers and sustained abstainers, improvements were most pronounced for symptoms scores (Table 5).

Lung Function

During the 1-year follow-up, FEV₁ deteriorated significantly in the failure group, whereas it was stable in the reducer group; the mean 1-year change in FEV₁ was –161 mL for failures and –5 mL for reducers (Table 6). In contrast, a statistically significant increase in FEV₁ (+60 mL, *p* = 0.048) was found in the sustained abstainers.

Weight Change

The mean weight changes at 1 year for subjects with complete follow-up were, as expected, much greater in sustained abstainers and reducers than in failures (Table 6). At 1 year, abstainers and reducers experienced clinically significant weight gains of 3.6 kg and 3.0 kg, respectively.

DISCUSSION

Efficacy of NRT for Smoking Cessation in COPD Patients

This is the first randomized, controlled trial to demonstrate the efficacy of NRT for smoking cessation in patients with all stages of COPD and also in smokers who consume <15 cigarettes per day. The main finding was more than a doubling of sustained abstinence rates with nicotine sublingual tablets vs placebo in a group of COPD patients with mild, moderate, and severe reduction in lung function. The actual 1-year quit rate of 14% with the nicotine sublingual tablet is in the same range as that reported in previous studies^{26,27} of NRT in healthy subjects performed by physicians in our group. The

Table 5—Change in SGRQ Score Between Baseline and 1 Year by Outcome Groups

| Outcome Groups | Patients, No.* | Symptoms Score | | Activity Score | | Impact Score | | Total Score | |
|----------------|----------------|--------------------|---------|------------------|---------|------------------|---------|-------------------|---------|
| | | Mean (95% CI) | p Value | Mean (95% CI) | p Value | Mean (95% CI) | p Value | Mean (95% CI) | p Value |
| Failures | 31 | –2.3 (–9.1–4.6) | 0.51 | –1.7 (–8.5–5.1) | 0.62 | –3.9 (–8.5–0.8) | 0.10 | –2.9 (–7.7–1.8) | 0.21 |
| Reducers | 46 | –20.6 (–27.3–13.9) | <0.00 | –8.2 (–12.8–3.6) | <0.00 | –4.9 (–8.7–1.1) | 0.01 | –8.5 (–12.2–4.8) | <0.00 |
| Abstainers | 36 | –28.6 (–35.4–21.7) | <0.00 | –6.3 (–12.1–0.6) | 0.03 | –8.0 (–12.6–3.5) | <0.00 | –10.9 (–15.5–6.4) | <0.00 |

*Patients who completed the 1-year follow-up according to study protocol (*n* = 113).

Table 6—Change in FEV₁ and Body Weight at 1 Year in Abstainers, Reducers, and Failures*

| Outcome Groups | Patients, No. | Mean FEV ₁ | | Mean Weight | |
|----------------|---------------|-----------------------|---------|--------------------|---------|
| | | mL (95% CI) | p Value | kg (95% CI) | p Value |
| Failures | 31 | − 161 (− 226–− 97) | < 0.00 | 1.06 (− 1.04–3.16) | 0.31 |
| Reducers | 46 | − 5 (− 67–57) | 0.88 | 2.97 (− 0.34–6.28) | 0.08 |
| Abstainers | 36 | 60 (1–119) | < 0.05 | 3.55 (1.80–5.20) | < 0.00 |

*All values were obtained 15 min after administration of 1.5 mg of terbutaline.

Lung Health Study²⁸ reported a 1-year point prevalence abstinence rate of 35% with nicotine gum in patients with early stage COPD, but there was a large difference in lung function between subjects in the Lung Health Study and our current study. In the Lung Health Study, the mean FEV₁ was 75% of predicted, *ie*, subjects enrolled were almost symptom free with very mild COPD (“healthy” smokers), as subjects who regularly used bronchodilators were excluded. In our study, the mean FEV₁ was much lower, 56% of predicted, *ie*, moderate or symptomatic COPD patients. It is generally believed that patients with mild COPD are more responsive to smoking cessation therapy compared to smokers with more severe COPD. Over time, this self-selection process leaves COPD smokers who are the most highly nicotine dependent, with the lowest motivation to quit. There is also some evidence that smokers with COPD are more nicotine dependent than healthy smokers.^{9,29,30} However, we did not find any relationship between lung function and success rate in a multinomial logistic regression analysis; this is in accordance with findings from a study^{8,30} of bupropion for smoking cessation in smokers with COPD, although the power in both studies may have been too weak to detect any link. One reason for the successful outcome with nicotine sublingual tablets in our study may be the relatively high number of tablets used daily during the first 2 months (approximately seven to nine per day), which was largely due to the focus on adequate dosage during training sessions.

We administered NRT to smokers with COPD irrespective of their baseline number of daily cigarettes, without any problems. The use of NRT in smokers who consume < 10 cigarettes per day has rarely been investigated, as one entry criterion in most studies of NRT is usually smoking at least 10 to 15 cigarettes daily.⁵ In the future, NRT should be recommended for smoking cessation for COPD patients who smoke, including “light” smokers. Experience from our clinic suggests that approximately one third of smokers with severe COPD have often reduced to < 10 cigarettes per day. As the pharmacokinetics of nicotine sublingual tablets are very

similar to those of nicotine chewing gum, and as the Cochrane review⁵ found odds ratios for quitting that were comparable for gum, patches, inhalers, and sublingual tablets, different forms of NRT should be administered according to patient and therapist preferences.

Both smoking cessation and reduction were associated with statistical and clinically relevant improvements in SGRQ in our study, although the improvement was greater in abstainers. This finding could be used as a motivational tool for smokers with COPD, and may persuade more reluctant smokers to quit, as they should expect a noticeable improvement in quality of life, particularly symptoms of COPD.

Effect of Behavioral Support

No statistically significant effect of more intensive behavioral support was observed in this study, although a doubling of the actual success rates was found in two of the three measures of abstinence for placebo-treated subjects. The total contact time during the initial 3-month treatment period was 95 min (45 min face-to-face during two clinic visits) in the low-support group, and 210 min (150 min face-to-face during four clinic visits) in the high-support group, with five telephone calls vs three telephone calls in the two groups, respectively. The number of contacts in each group during the initial treatment periods was fairly similar, and this might explain why no statistically significant effect was found for high vs low support. However, this finding offers a choice between two different treatment setups depending on local circumstances: either fewer visits, combined with proactive telephone counseling, or more clinic visits. One metaanalysis³ has documented the existence of a strong relationship between abstinence and the duration of each clinic visit, number of sessions, and total contact time, and also that proactive telephone counseling increases quit rates, while Cochrane metaanalyses^{5,31} only found a slight trend between support and quit rate. Both of our approaches could be classified as moderate support, and these were selected, as it is likely that more intensive support would be difficult to implement in

many chest clinics. However, the Lung Health Study²⁸ suggested that more intensive support combined with treatment for relapses appears to achieve higher quit rates than in the present study. In our study, all therapy was delivered by nurses as in previous studies^{32,33} published by our group, with no physicians directly involved in the therapy. There is evidence that smoking cessation services provide by nurses can be effective,^{34,35} and this is reflected in our findings.

One potential bias may have been the large early dropout of failures from the study. Consequently, these patients were not exposed to the possible effect of more intensive support. In our study, we reduced the potential bias of early dropout by contacting 79% of patients at the 1-year follow-up. The Lung Health Study²⁸ achieved a very high 1-year follow-up rate of 95%; this may partly be due to a strict initial selection of possible compliant subjects, as all participants had to pass three screening visits before entering the study. Integrating smoking cessation into the daily practice of COPD management may be a way of implementing the concept of recycling treatment failures and improving adherence to a smoking cessation program.

Smoking Reduction

We did not find any treatment effect of either nicotine sublingual tablets or behavioral support on smoking reduction, but 13% of the study population had reduced their daily cigarette smoking after 1 year. However, studies^{15,16} that have specifically examined the effect of NRT for smoking reduction enrolled smokers who were motivated to reduce smoking but who had low motivation to quit, and also used NRT for a longer duration (up to 12 months or 18 months). This may partly explain why NRT did not have any effect on reduction in the present study. Also, the main focus in our study was on smoking cessation. Nonetheless, the reduction in smoking in our study was remarkable as mean daily cigarette smoking at 12 months had reduced to four per day, with a corresponding low expired carbon monoxide level of 2 ppm, which was comparable with carbon monoxide values in abstainers. The reduction to this low number of cigarettes per day was also reflected in a weight gain of 3 kg among reducers, which was similar to the weight gain in abstainers (3.5 kg).

Lung Function Changes

Regarding changes in lung function, we observed a statistically significant increase in FEV₁ in abstainers of 60 mL after 1 year and a decrease in failures of 161 mL, which reflects earlier findings in the Lung Health Study³⁰ (an increase of 57 mL in abstainers

and decrease of 38 mL in failures). Findings from the Lung Health Study³⁶ suggest that a reduction in number of cigarettes does not affect lung function, but that a reduction to < 5 cigarettes per day might have a positive effect on the decline in FEV₁. This is probably why we found that FEV₁ did not decline in reducers in our study, who were smoking only four cigarettes per day at 1 year. In clinical practice, the positive effect of abstinence on FEV₁ might be another tool to further motivate this patient population to quit.

CONCLUSION

The results demonstrate that the use of sublingual nicotine tablets in conjunction with a nursing-run cessation program results in higher rates of smoking cessation compared to placebo. The quit rate achieved in our study was comparable to that achieved with NRT in "healthy smokers." NRT should be offered to patients with COPD as part of a smoking cessation program.

At this time, data are insufficient to draw conclusions about the relative efficacy of different forms of NRT in COPD patients, but prior studies³⁻⁷ in broader patient populations have suggested comparable efficacy for other forms of NRT. Patient preference, cost, and other variables should determine the most appropriate form of replacement therapy for a given COPD patient.

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