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Smoking cessation with four nicotine replacement regimes in a lung clinic

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ABSTRACT: Smoking cessation is a key intervention for prevention of several lung diseases. The aim of the present study was to compare the effect of smoking cessation with nicotine replacement in a lung clinic in a low resource set-up suitable for implementation in other lung clinics.

This was an open, randomized trial with 4 different nicotine replacement regimes combined with minimal behavioural support in daily routine. A total of 446 smokers (>9 cigarettes·day^{-1}) were allocated to a nurse-conducted smoking cessation programme with 4 treatment arms: a 5-mg nicotine patch ("placebo"), a 15-mg nicotine patch, nicotine inhaler, and a 15-mg nicotine patch plus nicotine inhaler. Recommended use of the nicotine products were 3 months with the possibility of continuing use up to 9 months on an individual basis. Individual follow-up studies were scheduled after 2 and 6 weeks, 3, 6, 9 and 12 months.

The 12-month point prevalence was 6% (5-mg patch (placebo)), 16% (15-mg patch) ($p<0.05$), 9% (inhaler) and 11% (15-mg patch plus inhaler), respectively.

To conclude, the set-up investigated in this study which included minimal behavioural support with nicotine patches should be evaluated in other lung clinics, as it doubled success rate when compared to a placebo with a 1-yr point prevalence of 16% and also the resources used are limited.

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Smoking is the main external preventable cause for the development of chronic obstructive pulmonary disease (COPD). Smoking cessation and long-term home oxygen treatment (for end stage disease) are the only treatments that affect the prognosis of COPD [1]. Nicotine addiction plays a prominent role in the persistence of smoking [2]. Nicotine replacement therapy (NRT) approximately doubles the 1-yr success rate in smoking cessation compared with a placebo [3].

As smoking involves both pharmacological and psychological factors receiving some degree of behavioural support is important, and as suspected the success rate increases with increasing intensity of behavioural therapy [4].

The highest success rates with NRT have been achieved in special smoking cessation clinics with 1-yr success rates of 25–35% as compared to success rates of 10% achieved in general practice with nicotine patches, however, NRT also doubled the success rate when compared to a placebo [5–8]. Nicotine patches, a fixed dose delivery system, which "infuses" approximately 1 mg of nicotine per h through the skin, are easy to use, and have shown an effect over a placebo in more than 20 studies even with minimal instruction in use [9].

Nicotine inhalers which deliver most of the nicotine into the mouth and throat, can be used *ad libitum* but this self-titration has both pros and cons. The advantages are that the inhaler can be used whenever a strong urge for a cigarette occurs and it may fulfil a need for hand-mouth-throat stimulation. The major disadvantage is nicotine underdosing. In three placebo-controlled trials the inhaler doubled the 1-yr success rate (15, 15 and 34% in active groups) [10, 13].

Increased short-term success rates have been observed in combination studies with nicotine patches and chewing gum [14–16]. However, the long-term success rates were not statistically significant after 6–12 months in any of the above studies. Thus, the authors decided to test the combination of the patch and inhaler. This combination was also chosen because the patch could serve as a provider of the basal nicotine substitution and the inhaler could be used whenever needed in "relapse situations" and to satisfy the behavioural aspects of cigarette smoking. It was suspected that this combination would lead to a higher success rate when compared to each method individually.

As this study was performed in a lung clinic, probably enrolling smokers with a low motivation to quit, it was assumed that the placebo could influence the entire study negatively. Therefore, a very low dose nicotine patch was used as a placebo (5-mg nicotine as the efficacy of a 7-mg nicotine patch was at the placebo level in another study [17]).

A major aim was to test a low resource design that could be easily implemented in other lung clinics. The efficacy of this setup was evaluated in an open, randomized study with 4 nicotine treatments including a: 5-mg nicotine patch, 15-mg nicotine patch, nicotine inhaler, and a 15-mg nicotine

patch plus a nicotine inhaler in consecutive smokers attending, a lung clinic after being referred for pulmonary problems.

Material and methods

Subjects and design

This was an open randomized study. The subjects were mostly referred from their general practitioner for a chest radiograph and/or lung function testing. A poster in the waiting room proclaimed that a trial was ongoing and that smoking habits would be recorded. The inclusion period was 24 weeks. Approximately 10,000 subjects attend the clinic per year.

The nurses completed the smoking records on all consecutive patients, and subjects smoking <10 cigarettes·day^{-1} were invited to participate in another smoking cessation trial based on a purely motivational approach [18].

Subjects smoking ≥10 cigarettes·day^{-1} were invited to participate in the present smoking cessation trial with nicotine replacement, but if they showed no interest in taking part they were invited to participate in the motivational study.

Inclusion criteria were smokers (>9 cigarettes·day^{-1}) aged 20–70 yrs, who were willing to quit smoking and use nicotine replacement (A "yes" answer to the question: "Would you like to quit smoking?") and who could also attend the clinic for follow-up studies. Exclusion criteria were suspicion of lung cancer or tuberculosis on the chest radiograph, senile subjects, noncooperative subjects and pregnant or lactating women.

Subjects included in the study were allocated to 1 of 4 treatment arms by a computer-generated list with random numbers. The treatment arms were: 5-mg nicotine patch, 15-mg nicotine patch, nicotine inhaler, and a 15-mg nicotine patch plus a nicotine inhaler. The NRT was recommended to be used for up to 3 months with the possibility of continuing treatment for up to 9 months on an individual basis. A nurse instructed the patients in how to use the nicotine products and informed them about the basic principles of how to quit smoking. A target-quit day was agreed during the next 2 weeks, and the patient was told to start with the NRT on quit day with daily use for 3 months. Follow-up studies were scheduled for 2 and 6 weeks, and 3, 6, 9 and 12 months after commencement of NRT. The subjects attended individual sessions lasting 15 min each.

At each follow-up smoking status was recorded, carbon monoxide levels were measured, a saliva sample was obtained for cotinine analysis, and use of NRT was recorded as well as any adverse events. The nicotine products were supplied free of charge up until the 9 monthly visit.

At a typical consultation day, three nurses examined 60 patients over 4 h in the lung clinic. Identified smokers were referred to a supplementary nurse after chest radiography and lung function testing, who then included the smoker in the study. Smoking patients saw the physician and were routinely advised to quit smoking.

At each visit the smoking cessation session lasted about 15 min and the case record forms were short and easy to complete. The nurses conducted all assessments, instructions, counselling and therapy.

After 1 yr all participants were contacted by telephone and abstinent subjects were invited to attend the clinic for carbon monoxide and cotinine assessments. Subjects who did not attend the clinic at scheduled visits were contacted by telephone and smoking status was recorded. They were requested to attend the clinic for follow-up studies. Subjects who either did not attend the clinic or were lost for follow-up were assumed to be smoking.

Nicotine products

Daytime patches: 5-mg and 15-mg nicotine patches were used for 16 h (Nicorette, Pharmacia & Upjohn, Helsingborg, Sweden). The maximal plasma nicotine concentration of 13 ng·mL^{-1} is attained after 8 h with the 15-mg nicotine patch. The patch was applied in the morning on the arm or in the hip region and removed at bedtime. The Nicotine inhalers consisted of a mouthpiece and a plastic nicotine container with, 10 mg of nicotine and the possibility of releasing up to 5 mg of nicotine when used (Nicorette, Pharmacia & Upjohn). A plasma concentration of 10–20 ng·mL^{-1} is attained in clinical use. The subjects were advised to use between 4 and 12 nicotine containers per day *ad libitum*. They were instructed to inhale deeply and to puff about 10 times more often when compared to smoking a cigarette. They were told to use the inhaler at least every hour except during sleep. All the participants received a booklet about smoking cessation and nicotine products at entry.

Assessments

Carbon monoxide in end-expiratory air after a 15-s breath holding exercise was measured at entry and at all follow-up studies with use of a carbon monoxide analyser (Bedfont Monitor, Bedfont Technical Instruments, Sittingbourne, UK). Subjects with carbon monoxide levels of <10 ppm (420 nmol·L^{-1}) were classified as nonsmokers [19]. They were also weighed on the same scale at entry and after 1 yr.

The self-completed paper-and-pencil Fagerström Questionnaire (FTQ) was used to measure each subjects degree of dependence on nicotine with a possible sum of 0–11 [20]. Also one question from the Fagerström Tolerance Nicotine Dependence questionnaire (FTND) was completed: "How soon after you wake do you smoke your first cigarette?"; 0–5 min: 3 points; 6–30 min: 2 points; 31–60 min: 1 point; after 60 min: 0 points [21]. The daily consumption of tobacco was recorded (cigarettes, cigars=5 cigarettes, cheroots=2 cigarettes, pipe, 1 g= 1 cigarette). The motivation to quit smoking was scored on a 6-point scale: 0=not at all; l=little; 2=some; 3=moderate; 4=much; 5=very much.

An unstimulated saliva sample *i.e.* Spontaneous spitting during 5–10 min without chewing (at least 3 mL) was collected in plastic cups and frozen at -20°C until it was to be analysed by gas chromatography for cotinine levels. Forced spirometry (Dry bellow spirometer; Vitalograph, Inc., KS, USA) was performed at entry according to the European Respiratory Society (ERS) guidelines [22]. The reference values used were those from a Danish population [23, 24].

Definition of outcome

The main outcome was a 1-yr point prevalence defined as no smoking during the last week of the 12 monthly visit plus a carbon monoxide level below 10 ppm. Secondary outcome was sustained abstinence, which included, self reported, no smoking after week 2, with no smoking at all between any visits, and a carbon monoxide level below 10 ppm at all visits. Abstinence with slips was defined the same as for sustained abstinence but with smoking at two separate occasions with consumption of up to 10 cigarettes in total. Carbon monoxide levels should be less than 10 ppm at all visits.

The study was conducted in accordance with the Declaration of Helsinki, and the local ethics committee with the approval of the Health Board.

Statistical analysis

Univariate one-way analyses of variance of all measured covariates were performed to test the success of the randomization procedure (a parametric test was used for normally distributed variables, otherwise the Kruskal-Wallis nonparametric test was used (table 1). Logistic regression was used to analyse the treatment effect at each follow-up visit using the placebo group as the reference group, (table 2 and table 3). A Cox-regression was used to analyse the treatment effect on the time to relapse, controlling for possible confounders among the covariates listed in table 1. All p-values were two-tailed, and $p \leq 0.05$ was considered a significant difference. Stata (Stata Statistical Software: Release 6.0. Stata Corporation, College Station, TX, USA) was used to perform all the statistical analyses.

Results

Two-thousand-one-hundred-and-forty eligible subjects attended the lung clinic in the trial period of which: 1,039 were smokers; 86 smokers would not participate at all; 197 smoked <10 cigarettes·day^{-1} and were included in the motivational study; of the 756 subjects smoking ≥10 cigarettes·day^{-1}; 310 would not participate in the present trial but agreed to participate in the motivational study; 446 subjects (59%) accepted to participate in the present study and were randomly allocated to the four treatment groups as shown in table 1 showing the demographic and lung function data.

The randomization procedure was successful for all variables, although the motivation to stop smoking tended to be a little lower in the "placebo" group compared with the 15-mg patch group, (table 1).

The average subject was ~50 yrs old, smoked a pack of cigarettes·day^{-1} and was moderately nicotine dependent with a FTQ of ~5.6 (table 1). Most subjects were apparently healthy without chronic lung disease. The lung function values were normal although nearer the lower limits of predicted values (table 1).

When the subjects relapsed, most would not attend the clinic again, resulting in an attendance rate of 68% after 2 weeks, 43% after 6 weeks, 28% after 12 weeks, and 11% after 1 yr. Most of those who did not show up at the follow-up studies were contacted by telephone and almost all had relapsed and were smoking again.

The 12-month point prevalence was 6% (5-mg patch (placebo)), 16% (15-mg patch) ($p<0.05$), 9% (inhaler) and 11% (15-mg patch plus inhaler), respectively. The percentage of sustained abstainers at each visit are shown in table 2. At 2 and 6 weeks the 15-mg nicotine patch and the combination of patch and inhaler were significantly more efficacious, compared to the very low dose patch. However, only the 15-mg nicotine patch maintained

Table 1. – Demographic data, lung function and smoking related data at entry

	5-mg Patch	15-mg Patch	Inhaler	Inhaler plus 15-mg Patch	ANOVA one-way p-value
Subjects n	109	104	118	115	
Age, yrs	49±13	50±12	48±10	50±13	0.64*
Males, %	50	46	46	43	0.84**
FTQ, 0–11	5.6	5.6	5.5	5.8	0.61**
FTND-A, 0–3	1.6	1.6	1.5	1.7	0.52**
Cigarettes·day^{-1}	18.8±7.3	18.1±5.5	18.1±6.8	19.3±7.5	0.51*
CO, ppm	18.8±9.4	19.0±9.6	19.5±7.4	19.9±9.8	
	N=105	N=104	N=113	N=113	0.80*
Cotinine ng·mL^{-1}	379±186	357±165	389±157	370±178	
	N=104	N=100	N=112	N=110	0.57*
Weight, kg	72.1±17.1	71.2±13.0	73.8±15.6	71.7±14.1	0.58*
FEV_1, L·s^{-1}***	2.85±0.92	2.88±0.90	2.89±1.00	2.70±1.01	0.41*
FEV_1 pred, %	85±20	89±21	86±21	83±21	0.21*
FVC, L	3.85±1.08	3.77±1.01	3.85±1.17	3.60±1.12	0.27*
FVC pred, %	91±18	91±17	90±18	87±16	0.26*
FEV_1/FVC, %	74±10	76±14	75±20	74±12	0.49*
Motivation 0–5	3.7	4.2	4.0	4.0	
	N=109	N=104	N=118	N=113	0.16*

Data are presented as mean±SD. *: parametric test; **: nonparametric (Kruskal-Wallis) test; ***: at body temperature and ambient pressure, and saturated with water vapour (gas). FTQ: Fagerström Tolerance Questionnaire; FTND-A: Fagerström Test of nicotine dependence; CO: carbon monoxide; FEV_1: forced expiratory volume in one second; pred: predicted; FVC: forced vital capacity; N: number of subjects tested from total.

Table 2. – Percentage sustained abstainers up to one year for the 4 different nicotine treatment arms

Time	5-mg Patch n=109	15-mg Patch n=104	Inhaler n=118	Inhaler + 15-mg Patch n=115
2 weeks	31.2 (34)	51.9 (54)*	36.4 (43)	59.1 (68)***
6 weeks	11.9 (12)	23.1 (24)*	16.9 (20)	24.3 (28)*
12 weeks	9.2 (10)	19.2 (20)*	13.6 (16)	14.8 (17)
24 weeks	6.4 (7)	14.4 (15)**	5.9 (7)	8.7 (10)
9 months	3.7 (4)	11.5 (12)*	5.1 (6)	4.3 (5)
12 months	1.8 (2)	8.7 (9)*	5.1 (6)	3.5 (4)

Data presented as % (n). *: p<0.05; **: p=0.061; ***: p<0.001.

Table 3. – Percentage success rate with slips allowed up to one year for the 4 different nicotine treatment arms

Time	5-mg Patch n=109	15-mg Patch n=104	Inhaler n=118	Inhaler + 15-mg Patch n=115
2 weeks	62.4 (68)	72.1 (75)	72.0 (85)	80.9 (93)*
6 weeks	22.0 (24)	43.3 (45)*	28.8 (34)	49.6 (57)***
12 weeks	14.7 (16)	33.7 (35)*	20.3 (24)	24.3 (28)**
24 weeks	8.3 (9)	19.2 (20)*	13.6 (16)	14.8 (17)
9 months	5.5 (6)	14.4 (15)*	6.8 (8)	7.0 (8)
12 months	2.8 (3)	11.5 (12)*	6.8 (8)	6.1 (7)

Data presented as % (n). *: p<0.05; **: p=0.071; ***: p<0.001.

superiority compared to the "placebo" up to 12 months (8.7% *versus* 1.8%, p<0.05, logistic regression).

The percentage of abstainers (when up to 2 slips were allowed) was as expected a little higher, that is 12% after 12 months for the 15-mg nicotine patch group and 3% for the 5-mg patch group (table 3).

Cox-regression analyses showed that high motivation, male sex, higher age, lower baseline cigarette consumption, lower baseline CO level, lower Fagerström Questionnaire score were all statistically significant pretreatment predictors of higher success. When controlling for these covariates as possible confounders, treatment decreased the hazard of relapse by 44% (15-mg patch), 25% (inhaler), and 49% (combination) respectively compared with the placebo treatment (5-mg patch), (table 4). Body-weight, cotinine, and lung function showed no statistically significant effect on outcome, and were therefore, not included in the analysis.

The degree of nicotine substitution was estimated by the use of saliva cotinine at entry and during treatment. In 66 of the 72 abstinent subjects, the overall degrees of substitution in the 3 active treatment groups after 2 weeks were 21–41%. No serious adverse events were reported.

Discussion

The main findings in this open study were that nicotine products increased success rate when compared to the "placebo" and that this low resource setup resulted in a 1-yr success rate of 16% (15-mg nicotine patch, point prevalence) compared with 6% for placebos.

The low success rate in the 5-mg nicotine group ("placebo") supports the fact that this group served as a placebo group, although bias such as negative expectancy to the efficacy of the low nicotine dose from patients and nurses might have contributed to the low outcome. The behavioural support was also minimal corresponding with the low overall success rate. In a placebo controlled trial carried out in the clinic with the nicotine patch, with more support than in the present trial, a 1-yr success rate of 11% *versus* 2% was found [25], which is in accordance with the present findings. Subjects allocated to the control arm in a parallel study in the lung clinic achieved a 1-yr success rate of 2% compared to 6% for the placebo in the present study suggesting that the setup *per se* influenced the outcome positively [18].

A 1-yr point prevalence success rate of 16% in the same range as that reported in 2 large placebo controlled trials in general practice [4, 5]. The setup in these and the present study is similar with minimal support and the inclusion of consecutive patients not especially motivated to quit smoking. In the present study the subjects attended the lung clinic to get a chest radiograph and some subjects might have felt a pressure to join the smoking cessation study. A higher success rate among self-referred smokers was expected. However, the motivation to quit was scored high, being given a value of 4 on a 0–5 scale, underlining the fact that the meaning of "motivation" is not very specific. Also, the participants had to quit within 2 weeks which may have been too short a time limit. In addition, the study would have been more adequate if there had been more frequent visits to the clinic during the first 6 weeks, as the majority of relapses occur during this period. However, compared to a recent study with much more support and with weekly sessions during the first 7 weeks, a 1-yr point prevalence of 16% was reported, the same as the findings in the present study [26].

In other studies, the combination of the nicotine gum and patch showed increased short-term outcome but no long-term superiority over either product separately. This is in contrast to a dose-response effect on success rate by increasing nicotine patch doses [7, 17].

Lung clinics could and should serve as a window of opportunity for the recruitment of smokers for smoking cessation [27, 28]. In a study performed in British chest clinics enrolling 1,550 patients with COPD physician advice alone or when given in combination with nicotine gum reported 1-yr success rates of 8.9 % and 9.8%, respectively with no effect from the nicotine gum [27].

In another study, in British chest clinics comprising 2,854 pulmonary patients, the physicians′ advice alone to quit resulted in a 5% quit rate after 1 yr with an increase to 13% when combined with 6 follow-up letters and 2 outpatient visits [28]. However, the quit rate in pulmonary patients cannot be directly compared with healthy subjects in the present study. In this study the physicians also advised the smokers to quit although more focus on the physicians role might have improved the outcome.

As most subjects referred from their General Practitioner are smokers with one or more lung symptoms but with almost normal lung function, it should still be possible to prevent development of COPD as well as other smoking related diseases in these subjects. An example of this is CEASE. It was one of the largest randomized placebo controlled smoking cessation studies up until now. Smokers (n=3,575) were treated with 0, 15 and 25 mg nicotine patches for 8 or 22 weeks [7]. The 1-yr success rate was 16.3% for 15-mg nicotine patch and 13.5% for placebo.

Table 4. – Cox-regression analysis of the treatment effect on the time to relapse controlled for pre-treatment predictors of abstinence

Variable	Hazard ratio	Standard error	Z-value	p-value	95% CI	
Treatments						
15-mg Patch*	0.56	0.08	-3.942	0.000	0.42	0.75
Inhaler*	0.75	0.11	-1.990	0.047	0.57	0.99
Combination*	0.51	0.07	-4.652	0.000	0.39	0.68
Pre-treatment predictors						
Motivation, 4–5/0–3$^{+,**}$	0.66	0.07	-3.808	0.000	0.53	0.82
FTQ, 1–point$^{+,***}$	1.06	0.03	2.294	0.022	1.01	1.12
CO, 10 ppm$^{+,***}$	1.16	0.07	2.600	0.009	1.04	1.30
Age, 10 yrs$^{+,***}$	0.89	0.04	-2.774	0.006	0.81	0.97
Cigarettes·day^{-1} >20/≤20^{+}	1.32	0.19	1.995	0.046	1.01	1.74
Sex, males/females	0.76	0.08	-2.703	0.007	0.62	0.93

*: treatment compared to placebo; $^{+}$: high motivation to quit compared with low motivation; $^{\#}$: FTQ, CO and age had linear effects; FTQ: Fagerström Tolerance Questionnaire.

This study was performed in 33 lung clinics all over Europe with the recruitment of "healthy" smokers through advertisements. The higher success rate in the placebo group in CEASE might reflect self-recruitment of eligible smokers with a higher motivation to quit compared with the present study.

In subjects with mild COPD, it has been possible to produce high long-term success rates as shown in the Lung Health Study. Smokers (n=5,887) with mild to moderate airway obstruction were enrolled in a multicentre randomized study of smoking intervention *versus* usual care and inhaled anticholinergic bronchodilator [29].

Initially, an intensive 12-session smoking cessation programme was scheduled with the use of nicotine chewing gum plus adjunctive behavioural modification with a relapse prevention program every 4 months during the 5 yrs. The cross-sectional quit rate was high in the intervention group: 34% after 1 yr and 37% after 5 yrs compared with 9% after 1 yr and 21% after 5 yrs in the usual care group, respectively.

Overall, this large well-conducted study showed that aggressive and intensive smoking cessation programs can produce high long-term quit rates in smokers with mild airway obstruction. The study also found that there is a reduced decline in forced expiratory volume in one second (FEV_1) supporting the fact that smoking cessation is the first and most important intervention in smokers with mild "subclinical COPD".

In the present study a design that could be implemented in other lung clinics with a limited demand for extra resources was tested. One nurse can treat more than 1,000 smokers per year by following the present design.

The study findings, regarding predictors of success showed that nicotine treatment, higher age, male sex, lower baseline cigarette consumption and lower baseline CO level to be predictors of higher success rates, this is in accordance with the findings of the CEASE trial [7]. Motivation was also a predictor using a very simple scale and should be evaluated in other studies. However, motivation might vary less among self-referred participants.

To conclude, the setup used in this study, which included minimal behavioural support with nicotine patches for 3 months, should be evaluated in other lung clinics as the 1-yr success rate is in the same range as that found in other smoking cessation studies with more intensive support and follow-up. The resources to this activity are relatively limited. The coal is that all smokers admitted to a lung clinic or department should be identified, advised to stop smoking and offered a smoking cessation program. This treatment is also very cost-effective [30].

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