Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up

Thorsteinn Blondal, Larus Jon Gudmundsson, Ingileif Olafsdottir, Gunnar Gustavsson, Ake Westin

Abstract

Objective To evaluate the efficacy of using a nicotine patch for 5 months with a nicotine nasal spray for 1 year.
Design Placebo controlled, double blind trial.
Setting Reykjavik health centre.
Subjects 237 smokers aged 22-66 years living in or around Reykjavik.
Interventions Nicotine patch for 5 months with nicotine nasal spray for 1 year (n = 118) or nicotine patch with placebo spray (n = 119). Treatment with patches included 15 mg of nicotine for 3 months, 10 mg for the fourth month, and 5 mg for the fifth month, whereas nicotine in the nasal spray was available for up to 1 year. Both groups received supportive treatment.
Main outcome measure Sustained abstinence from smoking.
Results The log rank test for 6 years ($\chi^2 = 8.5$, $P = 0.004$) shows a significant association between abstinence from smoking and type of treatment. Sustained abstinence rates for the patch and nasal spray group and patch only group were 51% *v* 35% after 6 weeks ($P = 0.011$ (χ^2), 95% confidence interval 1.17% to 3.32%), 37% *v* 25% after 3 months ($P = 0.045$, 1.01% to 3.08%), 31% *v* 16% after 6 months ($P = 0.005$, 1.27% to 4.50%), 27% *v* 11% after 12 months ($P = 0.001$, 1.50% to 6.14%), and 16% *v* 9% after 6 years ($P = 0.077$, 0.93% to 4.72%).
Conclusions Short and long term abstinence rates show that the combination of using a nicotine patch for 5 months with a nicotine nasal spray for 1 year is a more effective method of stopping smoking than using a patch only. The low percentage of participants using the nasal spray at 1 year, and the few relapses during the second year, suggest that it is not cost effective to use a nasal spray for longer than 7 months after stopping a patch.

Introduction

In controlled clinical trials of nicotine replacement therapy, 1 in 5 smokers remained abstinent after 1 year compared with 1 in 10 smokers who abstained in self administered cessation.[1] Better treatments for smoking cessation are clearly needed. In several controlled studies, the value of treatment with nicotine only has been proved,[2–4] but recent studies assessing the efficacy of treatment with nicotine by high dose nicotine patches gave different results.[5–7] In the Collaborative European Antismoking Evaluation study, evidence in favour of dose-response relations was found, but increasing the duration of patch use did not improve abstinence rates.[7] Few studies on smoking cessation have looked at the effect of combining two or more methods of providing nicotine, but those that are available seem to suggest a higher efficacy through using more or different ways of providing nicotine.[8–10]

The long term results of nicotine replacement therapy have not been studied extensively. One recent follow up study of a large multicentre trial on nicotine patches reported abstinence rates of up to 20% for 4 years in the patch group versus 7% in the placebo group.[11 12] The respective abstinence rates for 1 year were 29% and 10%. In another study, the abstinence rates for patch and placebo for 3 years were 10% and 3% respectively.[13] In a recently published study on nicotine nasal spray, the sustained abstinence rates for 3.5 years were 15% for the nasal spray and 6% for placebo.[14]

We evaluated the efficacy of using a nicotine patch for 5 months with a nicotine nasal spray for 1 year on smoking cessation. We studied the effects of a higher level of nicotine substitution thus obtained and of using a flexible method of providing nicotine with the fixed method of a patch. We followed up the participants after 6 years to assess the rates of abstinence from smoking after the prescription for nicotine had stopped.

Subjects and methods

Protocol

In November 1991 we started recruiting smokers from Reykjavik and the surrounding towns (total population about 150 000; smoking prevalence 34%) by advertisements in local papers and on television. We evaluated all respondents by interview at the baseline assessment. To be eligible for the study, respondents had to be aged 21-69 years and had to have smoked at least one cigarette per day for ≥3 years. We excluded those with a history of recent myocardial infarction, severe nasal allergy, or skin disease, and those who used smokeless tobacco, were currently misusing alcohol, or were pregnant or breast feeding.

We arranged contact with the participants on 10 occasions during the study and an additional follow up after 6 years. The first contact was the baseline

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assessment conducted 3-6 weeks before the participants were to stop smoking. This appointment was followed by an instructional meeting one day before the participants were to stop smoking. We divided the 239 participants into 12 heterogeneous subgroups of 17-25 subjects each. The participants in each subgroup were allocated either patch and nasal spray or patch and placebo spray. The participants attended four supportive group meetings 1, 8, 15, and 22 days after stopping smoking. All participants were scheduled for individual follow up at 6 weeks, and at 3, 6, 12, and 72 months. No participants were lost to follow up during the first year; those who relapsed, however, were contacted only by telephone at the 1 year follow up. After 6 years all participants who were abstinent at 1 year were contacted again by telephone. At that time two participants had died of cancer—one in each treatment group. Participants abstinent at the 6 year follow up came to the clinic for measurement of carbon monoxide concentrations.

The outcome measure was the duration of sustained abstinence. Participants were considered to be smokers if they had, after stopping smoking, taken a single puff of a cigarette, used other forms of tobacco, used a nicotine drug other than that prescribed, had a carbon monoxide concentration of ≥ 10 ppm, or were lost to follow up. No participants were classified as smokers solely on the basis of the non-attendance part of the smoking status criteria—that is, no subject was lost at any follow up. The time to relapse was calculated as the number of days from stopping smoking to the day of starting smoking. Carbon monoxide concentrations were measured at baseline and at all subsequent contacts, including follow up at 6 years, with a EC50 monitor (Bedfont Technical Instruments, Sittingborne, Kent).

Statistical analyses

We based the number of participants required for the efficacy analysis on a significance level of 5% using a one tailed test, a power of 90%, and there being 55% of participants in the patch and nasal spray group and 35% in the patch and placebo group; 105 participants were needed in each treatment group. To allow for withdrawals and protocol violations, however, we aimed to analyse 120 participants. We used two sided probability tests in all comparisons for more conclusive results, and we considered a P value of <0.05 as significant. All tests were performed with SPSS software.[15]

We used the χ^2 statistic to compare the proportions of abstainers in both groups at the various follow up times. To calculate the proportion of participants remaining abstinent over time, we compared the survival of the two groups using the Kaplan-Meier method. Whenever distribution of data made it possible, we carried out comparisons of continuous variables between the groups using parametrical *t* tests, and we used the Mann-Whitney rank sum test for data that were non-normally distributed.

Assignment

On the day before the participants were due to stop smoking, they were allocated their treatment by computer generated randomisation code at a local pharmacy. The nasal sprays—nicotine or placebo—were taken from boxes labelled A or B, but the bottles themselves were unlabelled. The pharmacy staff were blinded to the content of the bottles. To prevent switching of treatments among participants and to help protect blinding, the same treatment was on four separate occasions dispensed to four couples. The staff of the smoking clinic had no knowledge of the treatment assigned to each participant. A total of 239 subjects were randomised. Two subjects were excluded early in the trial without breaking the randomisation code. They had been assigned the patch and nicotine spray. One was unable to attend meetings because of illness, and the other refused to use the drugs and attend meetings, thus leaving a total of 237 participants.

Masking

Nasal sprays were dispensed in identical brown bottles containing a colourless solution of either nicotine or black pepper oleo resin (piperine). The nicotine spray delivered 0.5 mg of drug per dose. The randomisation code was kept at the pharmacy during the trial and not broken until the data entry and analysis were completed. Blinding among participants was successful. At the 1 year follow up we found no significant relation between type of treatment and the participants' responses, which proved they had been unable to guess their treatment. From previous experience, one of the authors (TB) knew beforehand that participants using nasal spray for more than 3-6 months were more likely to have been assigned the nicotine nasal spray rather than placebo nasal spray.

Table 1 Baseline characteristics of participants. Values are mean (SD) unless stated otherwise

Variables	Patch and nicotine spray (n=118)	Patch and placebo spray (n=119)
No of men	43	35
No of women	75	84
Mean age (years) (range)	41 (23-62)	43 (22-66)
Tobacco (g/day)	25.6 (15.7)	25.0 (10.9)
Mean Fagerstrom test of nicotine dependence (1-10)	5.7	5.7
Mean cotinine concentration (ng/ml) (range)	378 (107-1138)	341 (37-765)
Carbon monoxide (ppm)	24.6 (12.30)	24.7 (10.70)
Mean body weight (kg) (range)	72 (40-119)	71 (48-118)
No of participants with history of treatment for alcoholism (%)	19 (16.1)	22 (18.5)

Results

Table 1 shows the baseline characteristics of the participants, and figure 1 illustrates the flow of the participants through the trial.

Figure 2 shows the results of a Kaplan-Meier survival analysis for 6 years with the proportion of participants abstinent from smoking as the survival variable. The results of the log rank test ($\chi^2=8.5$, $P=0.004$) show a significant association between abstinence and type of treatment. Table 2 shows the percentage of participants abstinent from smoking at the various follow up times. After 6 years, 1 out of 6 participants was still abstinent in the treatment group compared with 1 out of 12 in the patch only group.

During the second year after the start of the study, one participant relapsed in the patch only group and three in the treatment group. During the next 4 years

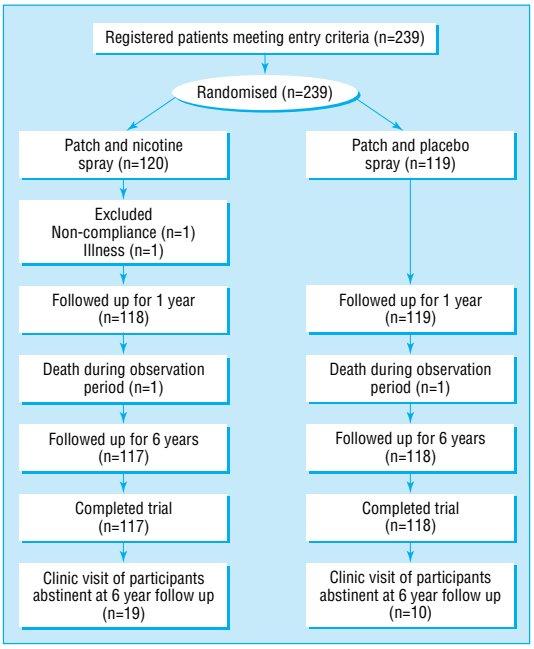

Fig 1 Flow of participants through trial

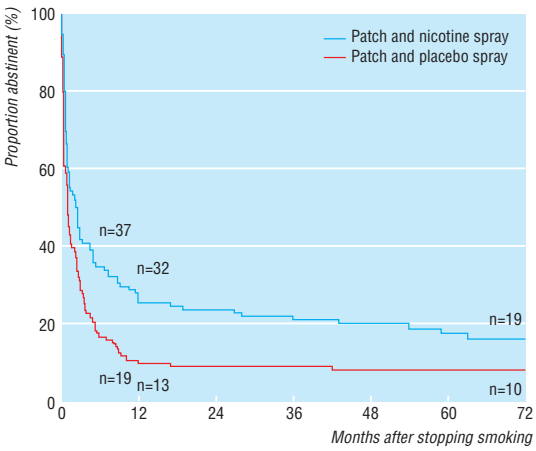

Fig 2 Kaplan-Meier survival curves showing difference in abstinence rates between participants allocated nicotine patch and nicotine nasal spray and those allocated nicotine patch only. Number of relapses during the 5 years was 12 *v* 2 in the treatment and patch only groups respectively (two abstinent participants died during the 6 year follow up period; one in each treatment group)

one participant relapsed and one died in the patch only group, and nine relapsed and one died in the treatment group.

Table 3 shows the proportion of participants using the spray among those still abstinent at the various follow up times, and the number of doses used in the treatment group and patch only group. Participants assigned the placebo spray used fewer doses and stopped taking the spray earlier than those assigned the nicotine nasal spray. At the 5 year follow up, 2 out of 22 (9.1%) participants in the treatment group were using nicotine chewing gum occasionally.

For the first 3 months, 91% or more of abstinent participants in either group used patches. During the following 2 months the participants discontinued patch use successively, and after 5 months the proportion was 25% to 30%. During the first 3 months only, the mean number of patches containing 15 mg of nicotine used by abstinent participants was significantly greater in the patch only group ($P = 0.038$) than in the treatment group.

Table 4 shows the level of substitution. In the treatment group the level of substitution ranged from 45% to 60% for the first 3 months versus 26% to 50% in the patch only group. Four participants with higher than average cotinine substitution concentrations (compared with mean blood concentrations at baseline) were still using nicotine nasal spray after 12 months. Of those four, one relapsed during the second year and two during the third year; the fourth participant remained abstinent throughout the study.

At the various follow up times during the first 3 months, the incidence of side effects (a yes or no answer) from patches ranged from 7% to 25% and were most often graded as mild on a scale from mild to moderate to severe. The most common side effects were itchiness and skin irritation. At the various follow up times during the first 3 months, the incidence of side effects from nicotine nasal spray ranged from 5% to 25% and were most often graded as mild or

Table 2 Percentage (number) of participants abstinent from smoking at follow up

Follow up	Patch and nicotine spray (n=118)	Patch and placebo spray (n=119)	P value (χ^2)	Odds ratio (95% CI)
1 day	88.1 (104)	82.4 (98)	0.210	1.59 (0.77 to 3.30)
15 days	70.3 (83)	52.1 (62)	0.004	2.18 (1.28 to 3.72)
43 days	50.8 (60)	34.5 (41)	0.011	1.97 (1.17 to 3.32)
3 months	37.3 (44)	25.2 (30)	0.045	1.76 (1.01 to 3.08)
6 months	31.4 (37)	16.0 (19)	0.005	2.40 (1.27 to 4.50)
1 year	27.1 (32)	10.9 (13)	0.001	3.03 (1.50 to 6.14)
6 years*	16.2 (19)	8.5 (10)	0.08	2.09 (0.93 to 4.72)

*Two subjects died, one in each treatment group, between 1 and 6 years of follow up: percentages calculated as 19/117 in treatment group and 10/118 in patch only group.

Table 3 Number of smokers abstaining at each follow up and percentage of abstainers using spray. Doses of self reported nasal spray (1 mg)

Period	Patch and nicotine spray (n=118)	Mean (SD)	Patch and placebo spray (n=119)	Mean (SD)
1 day	104 (89)	10 (6)	98 (92)	11 (7)
15 days	83 (77)	11 (7)	62 (68)	9 (6)
22 days	75 (64)	10 (7)	57 (54)	7 (6)
43 days	60 (52)	11 (7)	41 (39)	6 (5)
3 months	44 (39)	11 (8)	30 (20)	4 (1)
4 months	44 (23)	17 (9)	30 (3)	5 (0)
5 months	40 (28)	16 (9)	24 (4)	5 (0)
6 months	37 (24)	14 (9)	19 (5)	5 (0)
12 months	32 (13)	22 (9)	13 (0)	—

Table 4 Cotinine substitution concentrations

	Patch and nicotine spray			Patch and placebo spray		
Period	Users*	Mean	% of baseline cotinine†	Users*	Mean	% of baseline cotinine†
Baseline	111	378	100	111	341	100
1 day	94	227	60.1	90	170	49.9
15 days	61	171	45.2	56	128	37.5
43 days	31	192	50.8	38	136	39.9
3 months	16	191	50.5	27	88	25.8
6 months	8	226	59.8	0	0	0
12 months	4	495	131	0	0	0

*Those abstinent in respective treatment groups and using prescribed nicotine as either patch with nicotine nasal spray or patch only. At baseline, users refers to smokers.
†Percentages at each follow up derived from mean cotinine concentration at baseline.

moderate, but at follow up on day 1 after stopping smoking, 7 out of 22 participants with side effects graded theirs as severe. The most common side effect was nasal irritation.

Discussion

Our study shows that from day 15 after stopping smoking the use of a nicotine patch with a nicotine nasal spray is significantly more effective at stopping smoking than using a nicotine patch with placebo spray (fig 1, table 2). The difference in abstinence rates was double at 6 months and triple at 1 year, and after a further 5 years without nicotine replacement therapy the difference between treatment groups was double.

The participants in the treatment group had received an incentive over the patch only group by having access to nicotine nasal spray during the first year, thus alleviating smoking urges and giving them time to consider changes in self image. The almost triple difference in abstinence rates after 1 year ($P = 0.001$) can probably be explained by higher levels of substitution during the first 5 months (table 4), and particularly so during the remaining 7 months when only the treatment group had access to the nictoine spray, even if the spray was not always used daily (table 3).

The results suggest an increased efficacy in prevention of relapse with more intake of nicotine or by combining different nicotine replacement therapies.[8–12] Whether the quantitative or the qualitative aspect is more decisive can not be decided from the design of our study. Studies on dose-response relations of nicotine substitution have given different results.[7 16–18] The combination of a nicotine patch and nicotine nasal spray may have been successful not only because of the high level of substitution (table 4) but also because of the opportunity to respond quickly to the smoker's need.

Within the treatment group, 32 of the 118 participants (27%) were abstinent from smoking at 1 year and only 4 out of 32 were still using the nicotine nasal spray at that time. These four were, however, using high doses of nicotine throughout the study.

The 6 year abstinence rate in the treatment group was 16% versus 9% in the patch only group, a finding that shows the long term efficacy of treatment.

In one study of nicotine patches, continuous self reported abstinence rate at 4 years follow up was 20% for a patch with 21 mg of nicotine, 7% for placebo, and intermediate for patches with 14 mg and 7 mg of nicotine.[11] Our study confirms that by providing nicotine in several combinations, abstinence rates at 6 years can be double those of using a single method of nicotine replacement. It must still be acknowledged, however, that 7 out of 10 smokers relapse within the first year of stopping smoking.

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Contributors: TB and GG conceived the original idea for the study and wrote the protocol. IO and TB handled the group sessions and follow ups and helped collect the data. TB, LJG, and AW carried out the data analysis. The paper was written by TB and LJG. TB will act as guarantor for the paper.

Key messages

- Combined methods of nicotine replacement therapy have a potential advantage over one method because of high levels of substitution
- Nicotine patches release nicotine slowly, but nicotine nasal spray delivers nicotine more rapidly, enabling the smoker to respond quickly to any smoking urges
- Treatment with a patch and nicotine nasal spray was significantly more effective than patch and placebo from day 15 after stopping smoking
- Using a patch for 5 months with a nicotine nasal spray for 1 year provides a more effective means of stopping smoking than using a patch only
- It is not cost effective to use a nicotine nasal spray for longer than 7 months after stopping a patch

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Competing interests: TB was a consultant for Pharmacia and Upjohn, and GG and AW are employed by Pharmacia and Upjohn.

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Commentary: Progress on nicotine replacement therapy for smokers

John Stapleton

Four preparations for nicotine replacement therapy—chewing gum, skin patch, nasal spray, and buccal inhalator—have each been shown to approximately double a person's chance of stopping smoking.[1] Success rates are modest, however, with typically about 10-30% of smokers continuously abstinent for 1 year, depending on the quantity and quality of behavioural or counselling support.

One reason why success rates with nicotine replacement therapy are not higher is that no current formulation mimics the extremely rapid, rewarding, high arterial nicotine concentrations from inhaled tobacco smoke. A second possible explanation is underdosing. When used in standard doses all the products tend to give trough plasma nicotine concentrations, which are less than half of those a moderate to heavy smoker is accustomed to from cigarettes. Nicotine from the skin patch is absorbed into the bloodstream at a slow but steady rate throughout the day. The user has no control over dosing, but the patch is easy to use and ensures high compliance and reliable nicotine concentrations from the first day of use. Underdosing is mainly because the patch delivers less nicotine than smokers obtain during the daytime from cigarettes. Dosing with the nicotine chewing gum, nasal spray, and buccal inhalator is under the control of the user. Like smoking, their use includes some behavioural activity and provides sensory stimulation. They allow users to adjust the dose of nicotine as needed, albeit with less control and much more slowly than with cigarettes. Underdosing with these products is mainly because smokers cannot master the correct technique for their use, or because they find the irritant side effects unpleasant.

So far, results from studies of single preparations with increased nicotine doses have been disappointing. The only published large trial to examine the effect of doubling the patch dose (from 21 mg of nicotine per 24 hours to 42 mg per 24 hours) showed only a small transient benefit on smoking cessation over the standard dose.[2] Also, increasing the dose of nicotine in gum (from 2 mg to 4 mg per piece) has not proved universally advantageous in trials, although there is evidence of an additional benefit for more dependent smokers.[3]

Results from studies of the combined use of patch and gum seem to offer more promise. Two placebo controlled trials have been published, one showing an advantage of using the combined treatment over patch alone, the other over gum alone.[4 5] Blondal and colleagues' article reports on the first trial of a nicotine patch with nicotine nasal spray in smoking cessation. The combination produced nicotine replacement concentrations exceeding 50% of trough smoking concentrations, and was more than twice as effective as a patch with placebo spray. Pooling the results of the new study with those from the other combination trials gives an odds ratio of 12 month cessation for combination versus single treatment of 1.8 (95% confidence interval 1.2 to 2.8), that is, an improvement approximately equal to that for any single product for nicotine replacement therapy over placebo.

The new study is exceptional in following patients for 6 years and so provides much needed data on long term abstinence rates, and therefore the health benefits and cost effectiveness of a single course of nicotine replacement therapy.[6] There was still a clear advantage for the combination treatment after 6 years, with twice the number of successes, but 35% of abstainers at 1 year had relapsed by this time and the number needed to treat for each additional success with the combination consequently increased from 6 to 13. The nicotine nasal spray was used for up to 1 year in the trial, whereas the patch was phased out after 3 months. Since 57% of patients in the patch only group compared with 32% in the combination group relapsed between 3 months and 1 year, the extended period of spray use was clearly beneficial in preventing relapse during this period.

We cannot tell from this study how much of the success of the combined treatment was due to it providing higher concentrations of nicotine replacement, and how much was due to the flexible mode of delivery. The inclusion of a higher dose patch might have enlightened us, but such a design would have required a far larger study. Taken with evidence from other studies, however, this study supports the notion that higher concentrations of nicotine replacement are beneficial if they are achieved through allowing a degree of individual control over dosing, together with a reliable, if passive, method of delivering nicotine.

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Endpiece

The difference

The consultant is distinguished from the general practitioner less by the subtlety of his treatment than by the strength of conviction with which he executes it.

Thomas McKeown, *The role of medicine. Dream, mirage or nemesis?* (1979)

Submitted by Nicholas Steel, health services research fellow, University of East Anglia