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A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation

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A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. T. Blöndal, M. Franzon, A. Westin. ©ERS Journals Ltd 1997.

ABSTRACT: The objective of the study was to evaluate the therapeutic efficacy of nicotine nasal solution (NNS) for smoking cessation from the stopping day up to 3 months. We also followed the participants for 2 yrs after ceasing smoking to assess what happens after stopping using NNS.

In a placebo-controlled, double-blind, 2 yr prospective study, 157 smokers were given either NNS, one dose containing 1 mg of nicotine per 100 µL (n=79), or placebo (n=78). Treatment was continued for up to 1 yr.

One day after quitting smoking, the average number of daily doses was 11 in the group assigned NNS and 14 in the group assigned the placebo, and after 6 weeks, 14 and 6 doses, respectively, among abstinent participants still using spray. After 3 months, 65% of the abstainers in the nicotine group were still using the NNS. The abstinence rates were 51, 39 and 29% after 6 weeks, 3 and 6 months, respectively, as compared to 24, 19 and 18% in the placebo group (p=0.0003; p=0.003; p=0.050). The proportion abstinent at the 1 yr (25 *vs* 17%) and 2 yr follow-ups (19 *vs* 14%) was higher among those assigned to the nicotine than to the placebo group, but not significantly so for the numbers used in the study.

In conclusion, the use of nicotine nasal spray significantly increased the abstinence rate during the first 6 months following the quitting day.

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The use of nicotine combined with group support during the initial period after stopping smoking, has been shown to be of value in numerous investigations. Nicotine polacrilex gum and nicotine transdermal patches [1, 2] are well established as aids to smoking cessation. Other nicotine delivery systems include nasal spray [3–5], which has now been approved for use in 11 countries, and a nicotine inhaler [6].

The aim of this study was to investigate the effect of a nicotine nasal spray (NNS) in the withdrawal phase of smoking cessation. Nicotine absorption is slow from nicotine polacrilex gum and particularly so from the transdermal patch. The serum nicotine levels attained are far below pretreatment smoking levels. Serum nicotine levels in gum users are seldom more than one third those of smoking levels [1], while the nicotine from nasal sprays is absorbed sufficiently rapidly to produce subjective effects similar to those from smoking and produce blood levels of ~40% of the smoking range [3, 7].

We attempted to investigate the effect of nicotine nasal spray treatment for up to 3 months and to assess the abstinence rates up to 1 yr after stopping the use of nicotine spray (2 yrs after quitting smoking).

Methods

Subjects and randomization

Recruitment for the study was done by newspaper advertisement in the second half of 1989. To be eligible, subjects had to be 21–68 yrs old and had to smoke at least 1 cigarette·day^{-1}. Subjects had to be motivated to stop smoking and be willing to adhere to the trial protocol. The trial was conducted in accordance with the Helsinki declaration, as amended in Venice 1983, and was approved by the Ethics Committee of the University Hospital in Reykjavik. The criteria for exclusion were a history of recent myocardial infarction, severe allergy, current abuse of alcohol or other drugs, and pregnancy/breast-feeding. Use of psychoactive medications was not an exclusion criterion and neither was former nicotine replacement therapy (NRT). Those interested in participating were scheduled for an appointment and underwent initial screening by telephone. A total of 178 attended the screening interview in the clinic. Of those 178 initially found eligible, 158 attended the first group session, entered the trial and were randomized.

The study medication (nicotine or placebo) was dispensed by the University Hospital pharmacy. The subjects were assigned to either nicotine or placebo treatment according to a computer-generated randomization code. Seventy nine subjects were assigned the active treatment and 78 the placebo spray. One subject was excluded 1 week after randomization because of noncompliance with protocol requirements. During the first 6 weeks, supportive treatment was given during group sessions, with the 157 participants divided into seven heterogeneous groups, the participants in each group receiving either the nicotine spray or a placebo. Subjects and therapists were blind to treatment assignment.

Study population

The baseline characteristics of the study population are shown in table 1. The values for all variables were similar in both groups. Forty men and 39 women received nicotine treatment and 30 men and 48 women received the placebo.

Nasal nicotine spray (NNS)

The NNS device (supplied by Pharmacia & Upjohn Consumer Health Care, Helsingborg, Sweden) consisted of a pocket-sized, multidose bottle with a pump mechanism fitted to a nozzle for insertion into the nostril. The active spray delivered 0.5 mg of nicotine per 50 µL squirt. One dose consisted of two squirts, one into each nostril (a total of 1 mg of nicotine). The placebo spray contained black pepper oleo resin (piperine) to mimic the sensory effect of nicotine. Spray use was on an *ad libitum* basis, allowing up to a maximum of 5 doses·h^{-1} (5 mg of nicotine) and 40 doses·day^{-1} (40 mg of nicotine). A leaflet with an instructive picture was provided and emphasis was placed on teaching the correct technique for using the spray, which was repeatedly discussed at group sessions. Subjects were advised to use the spray whenever they felt an urge to smoke. The recommended duration of use was 3 months, but subjects who felt a need to continue beyond this time were strongly encouraged to do so. No nasal spray was dispensed after the 1 yr follow-up. Furthermore, no formal dose reduction scheme to wean subjects off the spray was imposed.

Group treatment and clinic visits

Supportive treatment consisted of six group sessions over 43 days, each lasting 1 h. A first preliminary meeting was held mainly to inform the subjects about nasal spray usage. Those who did not attend this meeting were not randomized. The day after this first group session was defined as the "quitting day" or "day zero". The next session took place one day after day zero and was followed by five group sessions, which were held 6, 8, 15, 22 and 43 days after day zero. Attendance at the six meetings was as follows: 98% (day 1), 99% (day 6), 85% (day 8), 76% (day 15), 68% (day 22) and 59% at the last group meeting, after 43 days. At these meetings, the need for a change in attitude towards smoking was emphasized. The supportive treatment was group-orientated and did not follow any formal behavioural scheme. At the sessions a comfortable atmosphere was created in which the participants could support each other and discuss various methods available to remain free of smoking and how to cope with difficult situations. All the participants received an instruction booklet on how to stop smoking. Individual follow-ups were carried out 3, 6, 12 and 24 months after the start of treatment. At these times, all of the subjects were contacted by telephone and those reporting abstinence were asked to attend a "validation appointment". Current smokers provided details by telephone only.

Table 1. – Baseline characteristics of the study population

Characteristics at entry	NNS group	Placebo group
Sex M/F	40/39	30/48
Age yrs	42 (22–67)	42 (21–67)
Amount smoked g·day^{-1}	26 (4–50)	24 (6–45)
Salival cotinine ng·mL^{-1}	410	430
Baseline CO ppm	29 (3–80)	29 (2–57)
FTQ	7.1 (3–10)	7.3 (4–10)
Duration of smoking 10 yr periods	2.7 (1–5)	2.7 (1–5)

Values are presented as absolute value, or as mean with range in parenthesis. NNS: nicotine nasal spray; M: male; F: female; FTQ: Fagerström Tolerance Questionnaire, an assessment of nicotine dependence, maximum 11.

Measures

During all visits up to 12 months, each subject was requested to fill in questionnaires on the number of cigarettes smoked between visits, the use of any nicotine treatment other than that prescribed and any adverse reactions, *i.e.* nose irritation, throat irritation, cough, sneezing, watery eyes, rhinorrhoea, palpitations, nausea, sweating, headache, any calming effect and dizziness. Each adverse reaction was graded as "mild", "moderate" or "severe" and the corresponding numeric score of 1, 2 and 3 was registered. Adding the score registered at each visit made up the total score for each adverse reaction. Any craving for cigarettes, along with reports of one or more of 10 other symptoms, (*i.e.* irritation, boredom, tiredness, dizziness, headache, increased appetite, difficulties in concentrating, sleep disturbances, lack of energy) and an open question about any other symptom, was also recorded at baseline and up to the 6 month follow-up. Each participant responded to the Fagerström Tolerance Questionnaire (FTQ), with an assessment of nicotine dependence, and was rated from zero to a maximum of 11 [8]. A visual analogue scale, with a rating from zero to 10, was used by the subjects to assess the usefulness of nasal spray treatment.

Verification of nonsmoking status

At the baseline assessment, subjects provided a smoking history. On the same occasion (and at all later visits) carbon monoxide (CO) was measured (using an EC50 monitor, Bedfont, Technical Instruments, Sittingbourne, UK). Subjects were instructed to inhale deeply and to hold their breath for 10–15 s before expiring with full force through the inflow valve of the monitor. Levels of 9 parts per million (ppm) or lower were considered to indicate a nonsmoking status [9]. Subjects were weighed (with indoor clothes but without shoes) at assessment, after 9 days, 6 weeks, and 3, 6, 12 and 24 months. The amount of nasal spray used was recorded in a daily diary and also at group sessions and individual follow-ups, along with any smoking that occurred between visits.

Determination of abstinence

The 157 subjects formed the base both of abstinence rates and the survival table analysis. At the follow-ups on days 1, 6, 8, 15, 22, 43, 91, 182, 365 and 730, the criterion for recording the "lapse free abstinence" (LFAT)

was continuous abstinence from day zero. The LFAT ended permanently (terminal event) if a subject started smoking on a daily, or occasional basis, or if a subject admitted using another nicotine replacement therapy, including nicotine gum and patch, during the study period. At the follow-up visits, nonsmoking claims were confirmed by a CO measurement of <10 ppm. One subject lost to follow-up was assumed to be a smoker. Subjects who failed to keep their appointments usually had resumed smoking and were contacted by telephone regularly at the follow-up times throughout the study. For the life table analysis, the day when LFAT stopped was registered for each subject.

Determination of cotinine in saliva

Cotinine is a major metabolite of nicotine and is a useful marker. A sample of at least 3 mL of unstimulated saliva was collected in a plastic cup at each visit, usually in the afternoon, sealed and frozen at -20°C, within 1 h. The saliva samples were analysed at the Pharmacia & Upjohn laboratory by gas chromatography [10, 11]. Throughout the study the measures of cotinine were not used to validate claims of abstinence, as this would have meant applying a more stringent criterion to the placebo than to the active group.

Statistical analysis

The study was designed to detect at least a 20% significant difference between active treatment and placebo at 3 months, with observation of abstinence rates for up to 1 yr. The observation time was later extended to include a 2 yr follow-up as well, although this was not originally planned. It was projected, from previous trials using nicotine replacement procedures, that the placebo would yield a success rate of about 15%, while the new treatment was expected to yield a rate of 35% (at 3 months). The minimum number of subjects was set to 2×56 to achieve a Type II error of 20% if the Type I error was 5%. The difference between active and placebo groups in abstinence rates at the different follow-up times was assessed by the chi-square test. For calculation of the proportion remaining abstinent over time, a life table procedure, which compared the survival of the subgroups, was performed [12]. For comparing variation among the means of more than two groups, multiple analysis of variance was used. In view of all the evidence suggesting the relative effectiveness of nicotine replacement, one-sided probability tests were used when comparing abstinence rates at the follow-up visits. In all other comparisons, two-sided probability tests were used. A p-value of less than 0.05 was considered significant.

Results

Abstinence

After one day, there was a significant difference in abstinence rates between the study groups. This difference was maintained at the follow-up visits up to 6 months after the quitting day, but not at the 1 and 2 yr follow-up visits (table 2). The rates of total abstinence for 6 weeks, 3 months and 6 months were 51, 39 and 29% in the nicotine spray group and 24, 19 and 18% in the placebo spray group respectively (p=0.0003; p=0.003; p=0.050). At the 2 yr follow-up, 19% of the participants receiving active treatment were found to have been completely abstinent throughout the 2 yr period, compared to 14% of the placebo participants.

The survival analysis, with the proportion abstinent as the survival variable, is shown in figure 1. Placebo subjects were less likely to maintain abstinence during the group session period than those on active therapy. The median survival at the 2 yr follow-up visit was 49 days among participants assigned nicotine *vs* 10 days for those assigned the placebo. Comparison of the survival experience in the two treatment groups, using the Wilcoxon (Gehan) statistic, yielded an average score of 22.2 for active and -22.5 for placebo groups, with a significance level of p=0.002.

Background factors

Age, initial level of tobacco consumption, cotinine levels, FTQ and initial carbon monoxide value were not related to type of therapy or to relapse in smoking, both after 43 days and after 2 yrs.

Table 2. – Percentage of participants abstinent* at follow-ups

Follow-up time	NNS (n=79) %	Placebo (n=78) %	p-value	Estimated relative risk 95% CL
1 day	94 (74)	82 (64)	0.013	3.24 1.11–9.48
6 days	73 (58)	58 (45)	0.020	2.03 1.03–3.96
8 days	71 (56)	53 (41)	0.009	2.20 1.14–4.24
15 days	59 (47)	40 (31)	0.007	2.23 1.18–4.22
22 days	59 (47)	26 (23)	<0.0001	3.51 1.81–6.81
43 days	51 (40)	24 (19)	0.0003	3.18 1.61–6.28
3 months	39 (31)	19 (15)	0.003	2.71 1.32–5.58
6 months	29 (23)	18 (14)	0.050	1.88 0.88–3.99
1 yr	25 (20)	17 (13)	0.092	1.69 0.78–3.71
2 yrs	19 (15)	14 (11)	0.205	1.42 0.61–3.34

*Continuous prevalence rates after day zero. No smoking and only prescribed nicotine permitted. Expired CO <10 parts per million (ppm) at follow-ups. Values are presented as percentage, with absolute number in parenthesis. NNS: nicotine nasal spray; 95% CL: 95% confidence limit.

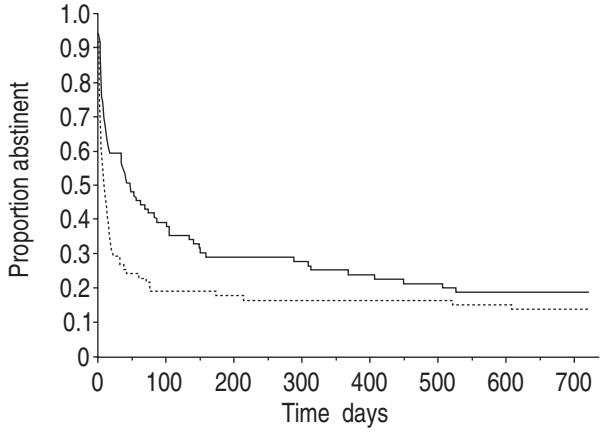

Fig. 1. – Proportion of abstinent subjects by day for 2 yrs. Those receiving the placebo (- - - - -) relapsed much sooner than those using the nicotine nasal spray (——).

Use of nasal spray

All participants used the spray they were assigned at least once. The proportion of abstinent subjects still using the spray and the average number of daily doses at each follow-up is shown in table 3. Among subjects assigned nicotine, the number of doses used remained high throughout the first year, after which no more NNS was dispensed. The percentage of total (n=79) NNS spray users was 25, 19 and 11% at 3, 6 and 12 months, respectively. The percentage of NNS spray users among the abstainers at each follow-up visit was 65, 65 and 45% respectively. For daily NNS users (≥1 dose·day^{-1}), mean salival levels of cotinine during the first 3 weeks were one quarter of baseline smoking levels. After 6 weeks and 3 months the substitution level was 32 and 46%, respectively (fig. 2). For the subjects remaining on the spray for longer time periods, levels of substitution were much higher (fig. 2). At 12 months, nine out of 20 abstainers in the active group (45%) were still using the NNS, averaging 24 doses·day^{-1}. Retrospectively, it was seen that these nine subjects had used more doses than the average throughout the study (at 7 days=17 doses, at 23 days=20 doses, at 3 months=23 doses and at 6 months=26 doses). During the second year of the study, when they no longer had access to NNS, four out of these nine resumed smoking. The proportion of abstinent placebo spray users dropped rapidly after the first 8 days, and at the 3 month follow-up visits no one in the placebo group was using the spray.

The helpfulness of the spray, compared to a cigarette (linear scale 0 to 10), was rated significantly higher by subjects who were assigned to using the active NNS spray than by subjects assigned to the placebo (table 4).

Table 3. – Proportion of abstinent nasal spray users in the two treatment groups and mean number of doses used per day

	NNS (n=79)			Placebo (n=78)		
Follow-up time days	Abst n	Using spray %	Dose	Abst n	Using spray %	Dose
1	74	100	11±8	63	98	14±10
6	58	97	13±8	45	98	17±9
8	56	91	14±8	41	93	14±9
15	47	89	14±9	31	74	15±8
22	46	83	14±10	23	57	14±9
43	40	73	14±13	19	42	6±5
91	31	65	20±17	15	0	-
182	23	65	21±15	14	0	-
365	20	45	24±15	13	0	-

Abst: abstainers; NNS: nicotine nasal spray. Dose: doses used, expressed as mean±SD doses·day^{-1}.

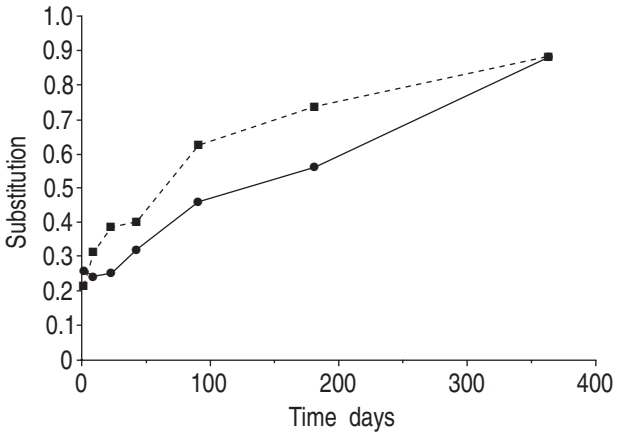

Fig. 2. – Level of substitution (of pretreatment salival cotinine 410 ng·mL^{-1}) in daily nicotine nasal spray (NNS) users at each follow-up (—●—) and in nine subjects still using NNS at the 12 month follow-up (- -■- -).

Tobacco withdrawal symptoms

Among all abstinent participants, the total score for withdrawal symptoms (a possible maximum of 44) reached a peak 2 days after quitting, as compared to the baseline score, and decreased between group meetings until day 22, when it had reached a plateau that remained essentially unchanged throughout the first year. Abstinent subjects on the active spray experienced fewer withdrawal symptoms at the first two group meetings after quitting (fig. 3) than did the participants on the placebo (t-test, p=0.01, 0.005).

Adverse effects

By adding the individual scores for the different adverse effects, a total score was obtained with a possible maximum of 36. Subjects on the active spray experienced more side-effects on the first day (p<0.001) after stopping smoking than the participants on the placebo (fig. 4).

Table 4. – How helpful was the nasal solution compared to a cigarette?

	NNS		Placebo		p-value
Follow-up time	n	Mean score*	n	Mean score*	(t-test)
1 day	73	5.9	62	3.9	0.001
6 days	53	6.1	41	3.9	0.001
8 days	44	6.5	32	4.6	0.005
15 days	36	7.2	19	4.9	0.005
22 days	35	6.5	13	5.5	0.277
43 days	24	7.6	7	4.2	0.002
3 months	19	8.4	2	3.7	0.003
6 months	15	9.1	0	-	
12 months	9	9.3	0	-	

*Score calculated using a linear scale of 0–10. NNS: nicotine nasal spray; n: number of subjects.

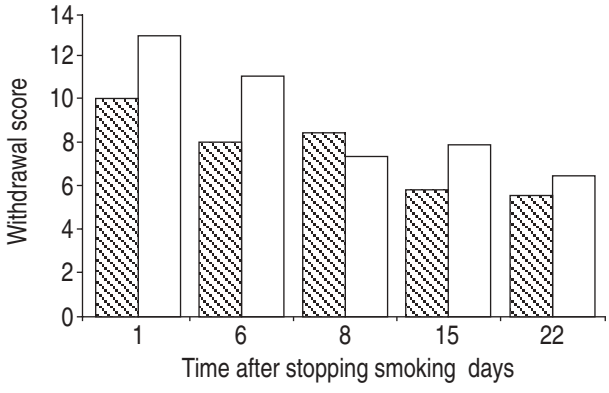

Fig. 3. – Withdrawal symptoms during the first 23 days after quitting. At the first two group sessions, the score was lower among subjects assigned to active NNS spray, but thereafter no significant difference in withdrawal score was noted between the groups. ▨ : nicotine nasal spray group; □ : placebo group.

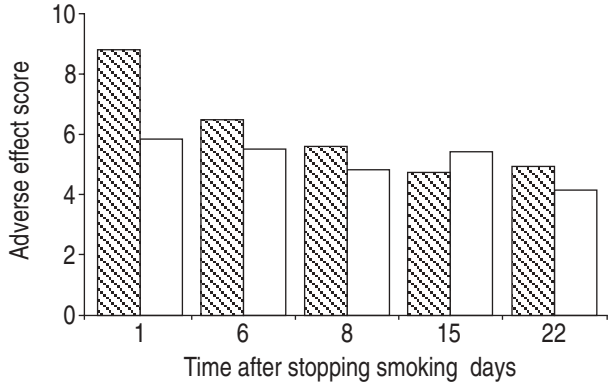

Fig. 4. – Total score of all adverse effects among nonsmoking spray users at each follow-up. After 1 day of use, adverse effects were more common in the nicotine group than among those using the placebo, but the difference levelled out during the first 6 days after quitting. ▨: nicotine nasal spray group; □: placebo group.

Among the subjects using NNS for a period of 6 weeks, adverse effects in general most often seemed to diminish with duration of use (table 5). After 1 day, 23% of the subjects rated the adverse effects as "no problem" and after 43 days of use the corresponding figure was 48%. After 1 day of use, 56% of the subjects labelled the adverse effects as "not serious" and after 43 days the figure was 48%; 18% of the participants recorded the adverse effects as "uncomfortable" after 1 day of use and only 4% after 43 days of use. Likewise, 3% of the subjects found the adverse effects to be "unacceptable" after 1 day whereas none of the participants rated the adverse effects as unacceptable after 43 days.

Among the placebo spray users, sweating was significantly more frequent at all five group meetings during the first 22 days of the study, and was the only side-effect more common in the placebo group.

Weight gain

Analysis of weight gain was confined to subjects abstaining from smoking at each follow-up. The mean weight gain in the subjects enjoying lapse-free abstinence at 3 months, 6 months, and 1 and 2 yrs after stopping smoking was 3.6 kg (4.7%), 5.3 kg (6.9%), 6.6 kg (8.3%) and 5.7 kg (7.4%) respectively. There was no difference in weight gain according to treatment.

Table 5. – Change in adverse effects in abstinent subjects using nicotine nasal spray (NNS) for full 6 weeks

Symptom	None		Mild		Moderate		Severe	
	1 day	6 weeks	1 day	6 weeks	1 day	6 weeks	1 day	6 weeks
Nasal irritation	13	24	46	48	36	7	5	0
Throat irritation	38	52	38	48	22	0	3	0
Coughing	61	86	18	14	21	0	0	0
Sneezing	28	44	36	48	33	8	3	0
Watery eyes	13	61	49	39	36	0	3	0
Runny nose	5	17	42	70	40	13	13	0
Palpitations	95	87	3	13	3	0	0	0
Nausea	95	91	5	4	0	4	0	0
Sweating	95	96	3	4	3	0	0	0
Headache	87	87	10	13	3	0	0	0
Calmness	44	44	31	35	26	22	0	0
Dizziness	80	96	18	4	3	0	0	0

Values indicate the percentage of subjects reporting symptoms, at the severity indicated, after 1 day (n=40) and 6 weeks (n=29).

Discussion

To our knowledge, this study is the fourth [3–5] to assess the efficacy of NNS in smoking cessation. What is interesting about these four studies is that the results are similar despite several differences in criteria (table 4). In the present study and the study of SCHNEIDER *et al*. [5], continuous abstinence from day zero was used to define abstinence, whereas in the study of HJALMARSON *et al*. [4], continuous abstinence from week 2 was used, and in the study of SUTHERLAND *et al*. [3] there was an initial 3 week period where slips were allowed. Supportive group treatment in the latter study consisted of six sessions over a period of 1 month. The number of group meetings in the study of HJALMARSON *et al*. [4] was eight over 6 weeks, while it was six meetings over 6 weeks in the present study, and none in the study of SCHNEIDER *et al*. [5]. All authors used 10 ppm in the carbon monoxide analysis as the cut-off limits for smokers except SCHNEIDER *et al*. [5], who used 9 ppm. All authors allowed use of NNS for up to 12 months, except SCHNEIDER *et al*. [5] who allowed NNS use until the 6 month follow-up. In addition, the entrance criteria of the four studies were not the same. The present study was the only one that allowed use of psychotropic drugs. In all four studies the use of nonprotocol nicotine was regarded as equivalent to smoking. The study of SCHNEIDER *et al*. [5] was the only one that required at least 15 cigarettes smoked·day^{-1} at entry and a minimum baseline value of 20 ppm of CO. Compared to pretreatment values the substitution level was 30–40% after 4–6 weeks and the number of doses·day^{-1} at that time was 13–15 in three of the studies. All the above-mentioned factors may account for differences in observed abstinence rates in the four studies (table 6).

The present study was designed to demonstrate differences in the study groups (NNS and placebo) up to at least 3 months. From the results (fig. 1, table 2), it is concluded that the use of NNS is a useful aid in smoking cessation. The effects of the NNS were even evident after only 1 day and persisted for at least 6 months. After 1 day, 100% of the abstainers were using the spray, at the 3 and 6 month follow-ups 65%, and at the 12 month follow-up 45%. The difference in efficacy was not significant at the 1 yr follow-up nor after 2 yrs, when all subjects had been off NNS for at least 1 yr.

The dose of NNS in the present study was self-titrated within the recommended limits (<40 mg·day^{-1}). The design of the study did not provide for possibilities for different treatments. However the results of the cotinine measurements suggest that pretreatment saliva cotinine levels (430 ng·mL^{-1} for the long-term NNS users) might be used in individual therapy to distinguish subjects who will need many doses of NNS (20–25 mg·day^{-1}) from those requiring few doses of NNS. The mean level of substitution after 6 weeks was only 40%, which is high compared to that obtained with other

Table 6. – Continuous abstinence rates (%) in four controlled trials of nicotine nasal spray (NNS)

Follow-up time	Present study (n=157)		Hjalmarsson *et al.* [4] (n=248)		Schneider *et al.* [5] (n=255)		Sutherland *et al.* [3] (n=227)	
	NNS	Placebo	NNS	Placebo	NNS	Placebo	NNS	Placebo
6 weeks	51	24	53	27	43	20	49	21†
3 months	39	19	41	20	34	13	41	17
6 months	29	18	35	15	25	10	32	12
12 months	25	17	27	15	18	8	26	10
24 months	19	14	-	-	-	-	-	-

†: Abstinence rate at 2 months.

NRTs but low compared to the baseline smoking levels.

The proper duration of NRT is not known. As Schneider *et al*. [5] point out, 3–6 months of NRT may not be enough to unlearn smoking behaviours after 20–40 yrs of practice and reinforcement. Given that other factors are controlled, smokers who are more dependent need treatment for a longer time. Since one key factor in stopping smoking is that the smoker must change his or her self-image to that of a nonsmoker, behavioural intervention and support is often vital. If behavioural intervention is successfully applied, there should therefore be less need for long-term NRT. Judging from the results of the 2 yr follow-up, we believe that for dependent smokers an appropriate recommendation should include 6–18 months of lapse-free abstinence before NRT is withdrawn.

In the present study, participants were encouraged to use NNS often enough over a sufficient period of time to be able to prevent a relapse. It should be noted that the NNS was dispensed without cost to the participants. Despite strong encouragement, it was not possible to persuade most of the participants to increase their use of NNS, either in quantity, or for a greater length of time. This approach is therefore not a feasible way to increase abstinence rates beyond those observed in this study. Therefore, the present focus on the combined use of different nicotine treatments and dosage patterns during therapy is a worthwhile approach [13–15]. The transdermal route is a fixed dose system with a low frequency of adverse effects. Gum and/or spray are more flexible drug delivery systems and ought to enable the subject to adapt nicotine use in response to mood changes during the day. Different delivery systems used in combination should be superior to a single system in bringing this about, particularly if the therapeutic ratio is more favourable with combination therapies. Patients on nicotine replacement therapy remain susceptible to relapse and must change their self-image to become true ex-smokers; otherwise, relapse is likely to occur upon stopping nicotine replacement therapy.

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