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Recycling of hard-core smokers with nicotine nasal spray

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Recycling of hard-core smokers with nicotine nasal spray. P. Tønnesen, K. Mikkelsen, J. Nørregaard, S. Jørgensen. ©ERS Journals Ltd 1996.

ABSTRACT: The primary aim of this smoking cessation study was to evaluate the effect of long-term treatment with nicotine nasal spray in a group of hard-core smokers. A further aim was to compare the effect of *ad libitum* with fixed dosage of nasal nicotine spray.

Eighty nine smokers, failures from two earlier studies with nicotine patches, were enrolled in an open smoking cessation study with nicotine nasal sprays, to be used *ad libitum* (n=45) or on a fixed schedule of 1 mg·h^{-1} during the day (n=44).

Carbon monoxide-verified continuous abstinence from smoking beyond Week 2, was 39% at 3 weeks, 12% at 3 months, 10% at 6 months and 6% after 1 yr, with no significant difference in success rate between *ad libitum* and fixed dosing. Mean daily nicotine dose was 15–16 mg during the first 3 months (range 2–65 mg). Tolerance to local irritating side-effects of nicotine developed during the first weeks of use.

Although short-term outcome was promising, the long-term success rate in this group of hard-core smokers was low. Other recycling set-ups are warranted, which might include more aggressive nicotine dosing.

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To attain an acceptable long-term success rate in smoking cessation, some basic principles have to be followed. The most important is that from the target quit day the smokers have to quit cigarettes completely; even a single cigarette on a few occasions ("slips") will probably lead to relapse.

The role of nicotine replacement with nicotine chewing gum and transdermal patches in smoking cessation has been established through several placebo-controlled clinical trials [1, 2], and a doubling of the success rate can be expected [3, 4]. The dose and the duration of nicotine replacement therapy has not been fully evaluated, though a duration of 6–12 weeks is recommended in most studies, and dose-response effects have been found for nicotine gum and patch [3]. The easiest nicotine product to use is the patch; when applied to the skin it releases about 1 mg of nicotine per hour, *i.e.* a fixed dosing system. Nicotine nasal spray (NNS), inhaler and gum have to be used *ad libitum* or prescribed to be taken every hour or so, with the possibility of self-regulating the dose when needed.

Trials comparing the four different nicotine formulations have not been performed. In a meta-analysis, comprising 17,703 subjects and 42 gum studies, nine patch studies, one NNS and one inhaler study, the odds rates of nicotine therapy compared with controls were 1.61 for gum, 2.07 for patch, 2.92 for NNS and 3.05 for inhaler [5]. The possible role of nasal aerosols in smoking cessation have been sparsely examined [6–9]. The NNS is the nicotine delivery system most closely like smoking cigarettes, due to the fast nicotine absorption from the nasal mucosa.

In two well-designed, controlled trials of NNS, comprising 227 and 248 smokers, the 1 year outcomes were 26 and 27% in the active group compared with 10 and 15% in the placebo groups [10, 11]. In one study, a nicotine substitution of 40% of the smoking level was attained after 1 month of NNS use and 79% after 1 year [10]. However, the nicotine level was measured 5 min after a 1 mg dose of NNS as peak concentrations, and thus might have substantially overestimated the degree of nicotine substitution. For the recalcitrant smoker in the present study, the advantages of the NNS might be induction of fast and high peak nicotine concentrations, and the possibility of using the NNS whenever needed as a rescue to suppress craving in high risk situations and, thus, prevent relapse to cigarettes.

As smoking cessation may be regarded as a cyclical process, recycling of failures from smoking cessation trials seems obvious in order to improve long-term outcome. In a previous recycling study, we treated 126 failures from an earlier placebo-controlled nicotine patch study with active nicotine patches and individualized the dose according to the smoking cotinine levels [12]. Although the success rate in the recycling study was 50% after 3 weeks of treatment, all former nicotine-treated subjects had relapsed within 6 months.

The primary aim of this study was to evaluate the success rate with long-term treatment with NNS in this group of primary/secondary failures (*i.e.* hard-core smokers) in smoking cessation. A further aim was to compare *ad libitum* with fixed dosage of NNS.

Methods

Subjects

All subjects were failures from two nicotine patch studies [12, 13]. The "original" patch study comprised 289 smokers, 145 received active nicotine and 145 had placebo patches [13]. After 1 year, 126 failures participated in an open recycling study with nicotine patches [12]. After 2 yrs, 244 subjects were still smokers, and they received an invitation to participate in the present study [14] (fig. 1).

Approximately 100 subjects attended the clinic and the 89 interested subjects were enrolled, 45 subjects were allocated to *ad libitum* dosing and 44 subjects to fixed dosing. Of the 89 subjects enrolled: 31 subjects had received active patch twice with an interval of 1 yr, *i.e*. originally and after 1 yr in the recycling study; 32 subjects had placebo patch followed by active patch; 14 subjects only had active patch once; and 12 subjects had received placebo patch once. Thus, 71% of the subjects had been recycled and relapsed twice, and 87% of the subjects had received active nicotine patch at least once.

Demographic data and smoking variables are presented in table 1. Most subjects were healthy (58%), but 13 suffered from chronic obstructive pulmonary disease (COPD), one had angina pectoris, three diabetes mellitus, three arterial hypertension, six bronchial asthma, and 11 had other diseases. Twenty eight subjects were on daily medication (15 bronchodilators, 10 hormones, including contraceptives, and 19 other drugs).

Study design

This was an open randomized study with active NNS. Inclusion criteria were: smokers willing to follow the protocol and motivated to quit smoking completely. Exclusion criteria were: pregnancy and breast-feeding, severe or symptomatic cardiovascular disease, severe or unstable asthma and COPD, chronic nasal disease, abuse of alcohol and drugs, regular use of psychotropic medication, and use of smokeless tobacco. Eight (or nine) visits during 1 year were planned (Week 0, 1, 2, 3 and 6, and months 3, 6, (9) and 12). The first visit to the clinic was the target quit day, when all subjects were told to stop smoking abruptly and to start using the NNS. At the first visit, a medical history was obtained and supportive written material delivered. At each session, the assessments were followed by group meetings with 10–12 participants lasting 20–40 min, chaired by one physician. Most time was devoted to round-table discussion, when the participants talked about their experience of quitting smoking and use of the NNS.

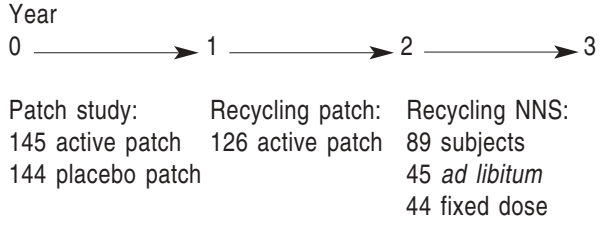

Fig. 1. – Study design. NNS: nicotine nasal spray.

Table 1. – Demographic data and smoking variables for the 89 subjects

Variable	Fixed dose n=44	*Ad libitum* n=45
Sex M/F	13/31	14/31
Age yrs	52 (14)	47 (13)
Cigarettes·day^{-1} n	22 (7)	22 (7)
Nicotine·cigarettes^{-1} mg*	1.6 (0.3)	1.5 (0.3)
Carbon monoxide ppm	22 (7)	26 (12)
FTND (0–10)	6.0 (1.9)	6.2 (2.0)
Saliva cotinine ng·mL^{-1}	472 (166)	455 (146)

Results are mean±SD. *: machine smoked nicotine delivery. M: male; F: female; FTND: Fagerström Tolerance Nicotine Dependence score.

Assessments

At each visit, smoking status was asked for, body weight was measured, and carbon monoxide was measured using a CO-analyser (Bedfont EC 50 CO Monitor, UK) in end-expiratory air after a 15 s breathhold [15]. An unstimulated salivary sample of at least 3 mL was collected in a plastic cup, stored at -20°C within 2 h, and later analysed for cotinine level by a fluorescence polarization immunoassay method [16].

At all visits, subjects were questioned as follows: 1) 14 withdrawal-related symptoms [17] for the last 24 h were scored on a five point scale: not at all=0, somewhat= 1, moderately so=2, very much so=3, markedly so= 4; 2) possible adverse events from the NNS scored as none, mild, moderate or severe, as judged by the patient.

The following scales were completed: 1) the Fagerström Tolerance Nicotine Dependence (FTND) Questionnaire [18]; 2) stress intensity (0–3) and frequency (0–3); 3) satisfaction with life during the preceding year (0–2); 4) motivation to quit (0–4); 5) fear of weight gain (0–4); 6) urge to smoke (0–4).

Nicotine therapy

The NNS (Pharmacia AB, Helsingborg, Sweden) consists of a hand-driven nasal pump spray. The bottle contains 10 mL of nicotine solution (10 mg·mL^{-1}) with a preservative. Each puff delivers 50 μL, equal to 0.5 mg of nicotine. Subjects were instructed to spray one puff into each nostril at each administration, *i.e*. a dose of 1 mg of nicotine.

Subjects were allocated to fixed dosing, *i.e*. 1 mg·h^{-1} when awake, or *ad libitum* dosing, *i.e*. up to 5 mg·h^{-1} and 40 mg·day^{-1} (80 puffs). Treatment should continue for 6 months, but tapering could be initiated after 3 months depending on the severity of withdrawal symptoms. Treatment could be continued for up to 12 months. The subjects registered the number of puffs used daily in a patient diary.

Measure of outcome

"Continuous abstainers" were defined as subjects completely abstinent from Week 2 until end-point and with a CO-level below 10 parts per million (ppm).

"Abstainers with slips" were defined as occasionally smoking between two visits, *i.e.* unlimited smoking for 24 h followed by up to 5 days of smoking less than 15% of the number of cigarettes smoked at entry, however, the CO-level should be below 10 ppm as above.

A subject not attending a visit was contacted by phone and eventually letter. Subjects lost to follow-up were assumed to be smokers. All randomized subjects were included in the outcome calculations.

Ethics

The study was approved by the local Ethics Committee and informed consent was obtained from all subjects.

Statistics

Demographic variables were described as mean and SD. Standard statistical tests were used, with a significance level of 0.05. Pearson Chi-squared test was used for categorical variables.

Results

The CO-verified sustained success rate plus/minus slips is shown in table 2. The 3 weeks success rate without slips was 39% declining to 6% at the 12 months follow-up, and 9% with slips allowed. There was no statistical difference in outcome at any time between the *ad libitum* and fixed dosing groups.

Table 2. – Success rates for the 89 subjects as sustained abstinence without and with slips (percent)

Time period	Sustained abstinence rate %					
	Without slips			With slips		
	Ad lib (45)	Fixed (44)	All (89)	*Ad lib* (45)	Fixed (44)	All (89)
3 weeks	40	39	39	56	57	56
6 weeks	27	20	24	44	41	43
3 months	16	912	27	18	23	
6 months	13	710	16	11	14	
12 months	7	5 6	9	7	9	

Numbers in brackets represent number of subjects.

Nicotine substitution, as measured by plasma cotinine, was 26–38% smoking levels (table 3) during the first 3 months. The participants used 15–16 doses daily during the first 3 months (range of 2–65). There was no difference between the two dosing regimens except for a tendency to a wider range of doses during the first 3 weeks in the *ad libitum* group.

Side-effects for the last 24 h at each visit appeared mainly as local irritating effects from nicotine in the nose, eyes and throat, decreasing during the first weeks (table 4). Moderate and severe side-effects are shown in table 4; however, 80% reported nasal irritation after 1 week of NNS use, declining to 61% after 2 weeks. On open-ended questions, nine subjects (10%) reported blood in nasal discharge and nose bleeding.

Systemic side-effects were few and nobody had to stop treatment with the NNS due to side-effects. However, two subjects disliked the NNS and only used it for 1–2 days. The increase in body weight in abstainers was 1.0 (SD 2.0) kg after 3 months, 3.0 (SD 3.8) kg ($p<0.05$) after 6 months, and 4.4 (SD 2.3) kg ($p<0.05$) after 12 months. No tendency to a lesser weight gain was found in daily users of the NNS.

As all subjects received active NNS, the influence on withdrawal symptoms cannot be properly evaluated. However, changes in score from smoking baseline compared with abstinence after 1 week showed increase

Table 4. – Moderate and severe side-effects from NNS use up to 6 weeks in percentage at each visit for the last 24 h

Symptom	Week 1 (n=74)	Week 2 (n=56)	Week 3 (n=50)	Week 6 (n=43)
Nasal irritation	23/22*	17/7	14/4	17/5
Pain in nose	20/22	17/9	10/2	9/5
Nasal blockage	7/4	2/2	4/4	7/2
Nasal discharge	16/19	18/9	12/2	14/0
Sneezing	16/6	9/4	6/2	7/0
Irritation in throat	8/10	4/2	6/2	5/0
Coughing	5/5	2/2	0/0	5/0
Watering eyes	8/7	2/2	0/2	0/0
Irritation in eyes	4/5	0/0	0/0	5/0
Palpitations	1/1	2/0	0/0	0/0
Cold sweat	0/0	0/2	0/0	0/0
Headache	1/4	2/2	0/0	10/0
Dizziness	3/0	0/0	0/0	0/0

*: 23/22=moderate in 23% and severe in 22%

Table 3. – Saliva cotinine concentrations and number of NNS doses daily up to 6 months in subjects with slips and in abstainers reporting daily use of NNS

	Subjects with slips				Abstinent subjects				All subjects	
		Cotinine conc. ng·mL^{-1}				Cotinine conc. ng·mL^{-1}			NNS	
Time	n	%*	mean	SD	n	%*	mean	SD	doses·day^{-1}	range
Entry	29	100	433	141	26	100	443	110	smoking	
1 week	29	52	230	90	26	26	116	76	16	2–65
2 weeks	12	30	140	88	38	28	125	95	16	2–50
3 weeks	15	35	174	102	31	31	136	103	16	3–40
6 weeks	11	31	134	67	24	29	138	66	16	7–52
3 months	5	58	327	222	14	38	160	117	15	3–30
6 months	1	119	437		4	14	58	73	6	3–15

One NNS dose=1 puff in each nostril, *i.e.* 1 mg nicotine. NNS: nicotine nasal spray. *: expressed as a percentage of the smoking value.

(approximately doubling) in the following symptoms: urge to smoke, irritability, impatience, restlessness, concentration difficulties, anger, depression, excessive hunger, and food intake above normal. The following symptoms were unchanged: headache, drowsiness, sleep disturbance, and anxiety. There was a decrease in insomnia. Scores were generally low, *i.e.* "urge to smoke": 0.60 increasing to 1.63 (scale 0–4); and "food intake above normal": 0.11 increasing to 0.90 as the extremes.

Stress was scored low ("How much stress": 23% not at all, 37% slightly, 23% some, 10% very much) ("How often": 35% almost never, 25% sometimes monthly, 22% sometimes weekly, 18% every day). Motivation to quit high was scored high (42% very much, 50% much, 8% moderate and slight). The concern about gain in body weight was relatively pronounced (36% very much concerned, 8% much, 15% moderate, 17% slight, 23% not at all). The answers on "satisfaction with life last year" were 39% very satisfied, 48% satisfied, and 13% not satisfied.

On the question "Will you succeed in quitting smoking?", 60% answered yes, 17% maybe, and 24% do not know.

Discussion

Recycling with NNS combined with psychological support showed a relatively low success rate, comparable with the success rate in our first recycling study with nicotine patches [12]. Excluding the 12 subjects who had only received placebo patch before - thus, only focusing on recycling of smokers who had received nicotine therapy before - reduces the 1 year success rate from 5.6 to 3.9%. The 3 month success rate in the present study (23%) was lower than original nicotine patch study (41%) ($p<0.01$), from which the present failures were recruited.

The 1 year result is also low compared with the 26, 27 and 27% in the three published studies with nicotine nasal spray [10, 11, 19]; however, it has to be remembered that our sample of smokers are failures from 1–2 earlier studies and, thus, should be regarded as "hard-core" smokers.

Undersubstitution with nicotine may have played a major role in the low success rate of the present study. The nicotine substitution attained was from 25–33% of the smoking levels, comparable with the substitution achieved using a low-dose nicotine patch [3, 13]. Two dosage regimens were used, however, no difference was observed between the fixed and *ad libitum* dosing group. With a mean daily dose of 16 mg nicotine, most subjects have in fact used the NNS once every hour as prescribed. In further studies, at least a doubling of dose should be tried as dose-response effects have been found for nicotine patches [20]. The cotinine levels attained with the NNS probably overestimate the "pharmacologically" active nicotine, as a variable amount of each puff in the nostrils is swallowed. On the other hand, plasma cotinine only reflects the cumulative dose of nicotine, but with the NNS the user attains fast and relatively high peak plasma nicotine levels 5–10 min after each dose, as reported by SUTHERLAND *et al*. [10]. Tolerance to the local side-effects of nicotine developed fast and most subjects could tolerate the NNS. However, it is important to give instruction and to let the subject try the first doses in the clinic under supervision, as the reaction to the first doses is usually severe, *i.e.* subjects often develop sudden sneezing, watery nasal discharge, strong burning sensation in the nose and coughing.

NNS should be tried in combination with nicotine patches, to ensure a basal substitution and still have the opportunity to use the "fast" nicotine dispenser, *i.e.* NNS. However, preliminary results from combined treatment with nicotine gum and patch have shown disappointing long-term results [21, 22]. Subjects were allowed to use the NNS up to one year in the above studies, thus longer treatment duration seems not to be the solution to improved outcome.

Besides the effect of the NNS, *i.e.* the pharmacological aspects of smoking dependence, the psychological factors might play an important role in the adherence to smoking in the present group of smokers. Regarding stress, withdrawal symptoms and motivation to quit, this group does not appear to be especially "difficult". The subjects own scoring of motivation was in fact high, and on the question "Do you believe you will quit smoking this time" 60% answered yes and 17% maybe, which could reflect a high degree of self-confidence. Also, in our clinical set-up, we incorporated much more behavioural and psychological group support compared with our previous studies.

As the smoking prevalence is decreasing in most European countries, the smoking population will contain an increasing proportion of hard-core smokers. Thus, it is relevant to conduct a larger randomized study with recycling of failures, focusing more specifically on psychological factors.

We have examined predictors of and reasons for relapse in the original patch study comprising 289 smokers, and found that previous attempts to quit smoking and low smoking saliva cotinine levels were associated with 6 weeks abstinence [23]. Also, "slips" was a significant predictor of relapse, and we focused on how to prevent slips in our group sessions.

Although a 6% 1 year sustained abstinence rate seems disappointingly low, it has to be remembered that the "spontaneous" quit rate in the general population is approximately 1% yearly. Our model of recycling should be tested by others before the recycling concept is dropped. More intensive adjunctive behavioural therapy might be valuable in subjects primarily treated with nicotine. Also, individualization of nicotine replacement therapy might improve outcome. There is a lack of studies comparing the results of different nicotine formulations (*i.e.* patch, gum, nicotine nasal spray, inhaler) and also of studies combining the different nicotine formulations [24].

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