Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up

Poul Wennike[1], Tobias Danielsson[2], Björn Landfeldt[2], Åke Westin[2] & Philip Tønnesen[1]

[1]Department of Pulmonary Medicine, Gentofte University Hospital, Copenhagen, Denmark and [2]Pharmacia AB, Consumer Healthcare, Helsingborg, Sweden

Correspondence to:
P. Tønnesen
Department of Pulmonary Medicine
Gentofte University Hospital
Niels Andersensvej 65
DK-2900 Hellerup
Denmark
Tel: +45 39 77 35 08
Fax: +45 39 77 76 28
E-mail: philipt@dadlnet.dk

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ABSTRACT

Aim To test the effect of nicotine gum and placebo in smokers not motivated or not able to quit smoking with regard to smoking reduction and smoking cessation.

Design This randomized study evaluated nicotine gum versus placebo for up to 1 year in 411 healthy smokers highly motivated to reduce cigarette use. Smoking reduction was defined as self-reported daily smoking less than 50% of baseline and any decrease (1 p.p.m. or more) in carbon monoxide.

Setting Pulmonary department, Copenhagen, Denmark.

Findings The overall success rate for sustained smoking reduction was significantly higher at all time-points for active versus placebo gum (6.3% versus 0.5% after 24 months). Nicotine gum achieved significantly higher point prevalence cessation rates than placebo at 12 and 24 months [11.2% versus 3.9% (odds ratio = 3.1; 95% CI, 1.4–7.2 and 9.3% versus 3.4% (odds ratio = 2.9; 95% CI, 1.2–7.1), respectively]. There was a linear relationship between decrease in number of daily cigarettes and decrease in plasma cotinine, exhaled carbon monoxide and plasma thiocyanate, with significantly greater reduction in the nicotine gum group after 4 and 12 months (maximum treatment duration) but not after 24 months. The decrease in toxin intake was smaller than the decline in daily cigarette consumption, suggesting that compensatory smoking occurred.

Conclusions Nicotine gum promoted cessation in this population of smokers unwilling to quit. Among reducers, the toxin intake correlated with reduced cigarette consumption although some compensatory smoking occurred.

KEYWORDS Carbon monoxide, cotinine, nicotine gum, smoking cessation, smoking reduction, thiocyanate.

INTRODUCTION

Smoking reduction is a highly controversial area given renewed interest during the last few years (Jimenez-Ruiz, Kunze & Fagerström 1998). In a clinical setting the smoking cessation rate after 1 year with nicotine replacement therapy (NRT) is in the range of 10–25% (Fiore *et al.* 2000; Silagy *et al.* 2001). For those smokers who, despite numerous quit attempts, are unable to stop or smokers with low motivation to quit, the concept of smoking reduction, i.e. decreased number of daily cigarettes smoked, may be an alternative approach to controlling their smoking. However, there is a need for data to examine whether smoking reduction can be maintained over time and if it facilitates smoking cessation (Hughes 2000).

One randomized, placebo-controlled study of 400 smokers who used nicotine or placebo inhalers reported a low but significant sustained reduction (defined as reducing cigarette consumption by at least 50% compared to

baseline) after 2 years (active 9.5% versus placebo 3%) (Bolliger *et al.* 2000). There was no statistically significant difference in point prevalence abstinence between active and placebo group beyond month 4. Nevertheless, almost 10% of subjects were smoke-free after 2 years.

The primary objective of this randomized, placebo-controlled study was to test the efficacy of nicotine gum in smoking reduction from week 6 to months 4, 12 and 24, respectively. This study also investigated whether smoking reduction leads to smoking cessation, changes motivation to quit smoking and affects cigarette toxin intake.

As smokers might compensate for the decrease in the number of cigarettes by increased inhalation, assessment of biochemical parameters of toxin inhalation is important in studies of smoking reduction (Benowitz *et al.* 1986; Hurt *et al.* 2000).

MATERIALS AND METHODS

Study design

This 2-year, double-blind, randomized, placebo-controlled trial with parallel groups tested the efficacy and safety of nicotine gum in smoking reduction. Subjects who scored 5 or less in the Fagerström Test for Nicotine Dependence (FTND) were allocated to the low-dose group and randomized to either nicotine 2 mg gum or placebo whereas those who scored 6–10 were allocated to the high-dose group and randomized to nicotine 4 mg gum or placebo (Fig. 1) (Tønnesen *et al.* 1988a, 1988b). Treatment was free of charge and provided for *ad libitum* use for up to 12 months. Thus, the last 12 months of the study participants were off medication.

A total of nine clinic visits on an individual basis were scheduled: baseline, weeks 2, 6, 10 and months 4, 6, 9, 12 and 24. Each visit lasted 15–30 minutes. All intervention groups received moderate behavioural smoking reduction information, and the general implications of smoking and its effects on health parameters were discussed. Subjects were asked to reduce their daily number of cigarettes as much as possible. Information was given to all subjects about possible ways to achieve this; increased interval between cigarettes, longer time to first cigarette in the morning, removal of habitual cigarettes. Smoking cessation was recommended as the ultimate goal throughout the study, but was not mandatory. The study protocol was approved by the Copenhagen County Ethical Committee and the Danish Health Board, and all subjects provided informed consent.

Study population

Subjects were recruited through newspaper advertisements. In order to achieve a total of 400 subjects, 590 subjects were screened over the telephone and the first 420 were invited to the baseline visit. Of these, 411 subjects attended and were enrolled in the trial.

The advertisement asked for healthy smokers who were unwilling or unable to quit smoking, but interested in reducing their smoking—with no intention to quit smoking within the next month.

Subjects were eligible to participate in the study if they fulfilled the following criteria: aged 18 years or older, were currently smoking ≥15 cigarettes/day, had smoked regularly ≥3 years, had an exhaled carbon monoxide (CO) level ≥15 p.p.m. after at least 15 smoke-free minutes, had failed at least one serious quit attempt within the last 24 months and wanted to reduce smoking as much as possible with the help of nicotine gum.

Subjects were excluded from the trial for any of the following reasons: current use of NRT or any other behavioural or pharmacological smoking cessation/reduction programme, use of other nicotine-containing products such as cigars, pipes or snuff, having unstable angina

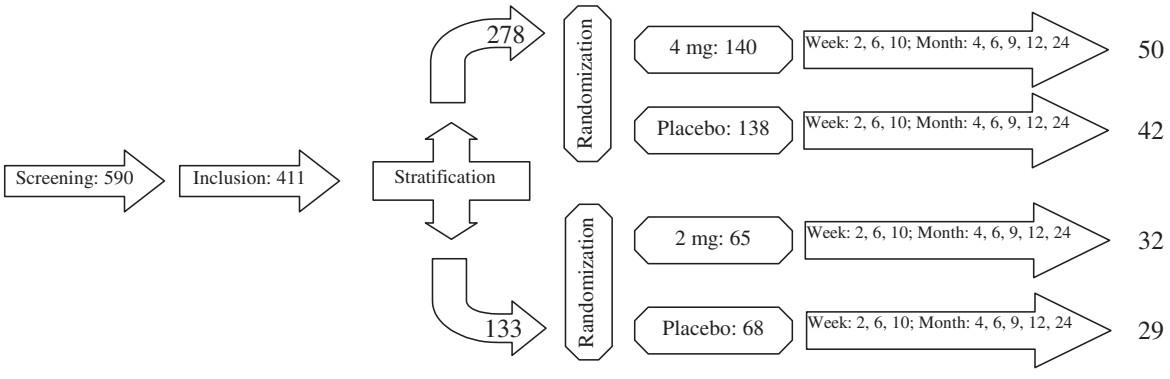

Figure 1 Diagram of study design. Stratification was performed on the basis of subjects' tobacco dependence. Subjects with a dependence score of 6 or more (n = 278) were allocated to the high-dose group. The numbers to the right represents the number of subjects (n = 153) who completed the study

pectoris, myocardial infarction within the last 3 months, under psychiatric care or medication, or alcohol or other drug problem that could interfere with the study or intention to quit smoking within the next month.

Treatment

Each piece of nicotine chewing gum (Nicorette®) contained either 2 mg or 4 mg of nicotine bound to an ion-exchange resin, which permits slow release of the nicotine, and alkaline hydrocarbonate buffer that increases buccal absorption of nicotine by increasing salivary pH to 8.5. The bioavailability of nicotine from the 2 mg and 4 mg gum is approximately 50%. The placebo gum was similar in appearance and taste, but contained no nicotine.

Assessments

The main assessments were performed at entry and after 4, 12 and 24 months. All data were entered directly into a PC-based data entry program.

The primary outcome measure was reduction in daily number of cigarettes smoked by at least 50% compared to baseline from week 6 to months 4, 12 and 24, which had to be verified by any reduction (1 p.p.m. or more) in expired CO compared to baseline. The question 'How many cigarettes do you smoke per day as an average?' was used to assess subjects' self-report of cigarette consumption. Point prevalence smoking reduction or cessation refers to subjects' smoking status at the visit. Subjects answering 'Yes' to the question 'Have you stopped smoking'? and presenting a CO measurement of less than 10 p.p.m. were classified as abstainers.

Venous blood was drawn at baseline and after 4, 12 and 24 months. Plasma levels of cotinine and thiocyanate (Jarvis *et al.* 1987; Westley 1987; Velicer *et al.* 1992; Lindqvist *et al.* 2002) were analysed at Pharmacia AB, Consumer Healthcare, Helsingborg, Sweden.

Expired CO levels were measured using a CO analyser (Bedfont Smokerlyzer, Sittingbourne, UK). Any subject with a CO level ≥10 p.p.m. was categorized as a smoker (Jarvis, Russell & Saloojee 1980). In our definition of reduction of cigarette smoking, any decrease from baseline CO was confirmatory.

Changes in attitudes to quitting smoking were assessed throughout the study. At each visit, subjects were asked an open-ended question to elicit information regarding any adverse events.

Statistical analysis

Based on previous results in smoking reduction studies it was assumed that about 200 subjects in each group (active and placebo) were needed for a power of 80% and a two-tailed significance level of 0.05.

The primary analysis was an intention-to-treat analysis that included all subjects who were randomized and received medication. Dropouts were regarded as treatment failures. The primary analysis included abstainers.

All statistical methods were two-tailed and at the 5% significance level. No formal adjustments for multiplicity were performed, but *P*-values are presented for each test to allow for relevant interpretation. Furthermore, corresponding confidence intervals were calculated when appropriate.

The χ^2 test was used for categorical or binary variables, and the two-sided Mann–Whitney *U*-test for small and not normally distributed data.

RESULTS

Study population

A total of 411 smokers attended the entry visit and were randomized to receive either active gum ($n = 205$) or placebo ($n = 206$). Of these, 169 subjects (41%) attended the 12-month visit and 153 (37%) completed the 24-month study. The 258 subjects who stopped prematurely gave the following reasons: did not want to continue in the study ($n = 164$), lost to follow-up ($n = 67$) and adverse events or study protocol violation ($n = 27$). The 164 subjects (placebo 90 versus active 74, NS), that withdrew from the study because they 'did not want to continue' differed from those who continued in the study only in that they had a statistically higher FTND score at baseline: 6.8 compared to 6.2 and were on average 2 years younger.

Baseline characteristics

The smokers enrolled had a mean baseline consumption of 24 cigarettes per day, a mean CO of 28 p.p.m and a high degree of nicotine dependence (Table 1). A majority (61%) of subjects had made two to five previous quit attempts. Motivation to reduce smoking was high, with a mean score of 9.3 on a 10-point visual analogue scale. Two-thirds (68%) of the subjects were classified as highly dependent and allocated to the high-dose group. Forty-two per cent had used nicotine gum before.

Smoking reduction and smoking cessation

Treatment with nicotine gum was superior to placebo in achieving sustained smoking reduction including cessation throughout the study. There was also a statistically significant difference between treatment groups for point prevalence smoking reduction at 4 and 12 months but

not at month 24. A statistically significant difference in cessation was observed for nicotine gum compared with placebo at all time-points, with a point prevalence cessation rate of 9.3% versus 3.4% at month 24 (Table 2).

The numbers needed to treat (NNT) to help one subject to reduce smoking by at least 50% from week 6 to months 4, 12 and 24 are 11 (95% CI: 7–31), 14 (95% CI: 9–32) and 17 (95% CI: 11–42), respectively. The corresponding NNTs for point prevalence abstinence at 4, 12 and 24 months are: 17 (95% CI: 11–42), 14 (95% CI: 8–44) and 17 (95% CI: 9–84), respectively.

Biochemical measures of reduction

The reductions in cigarette consumption, exhaled CO and plasma thiocyanate were significantly greater in the nicotine gum group than in the placebo group after 4 and 12 months for all subjects still in the study, but there was no statistical difference after 24 months (Table 3). Failures are also included in these analyses.

In the active group at month 12, while still using nicotine gum, mean cigarette consumption was 46% of baseline value, while mean CO was reduced to 62%; plasma cotinine to 93% and plasma thiocyanate to 75% of baseline. Since the active treatment group obtained nicotine from both cigarettes and NRT, cotinine was more reduced in the placebo group even though the difference was not statistically significant after month 4 (Table 3).

A *post-hoc* analysis classifying subjects as abstainers, reducers and smokers (Table 4) showed that the reduction in number of cigarettes was followed by a small decrease in three measures of cigarette smoke inhalation (expired carbon monoxide, plasma cotinine and plasma thiocyanate). Subjects who reduced their daily cigarette consumption by 25–50% of baseline consumption had similar levels of CO and thiocyanate as those defined as smokers (i.e. cigarette reduction less than 25% of baseline) but had a lower plasma cotinine level.

Analysing the percentage reduction of number of cigarettes as a continuous variable versus change in CO ($R^2 = 0.47$, $P < 0.001$), cotinine ($R^2 = 0.30$, $P < 0.001$) and thiocyanate ($R^2 = 0.38$, $P < 0.001$) showed a linear relationship for all three variables after 24 months.

Table 1 Baseline characteristics of the 411 smokers enrolled; values are expressed as means (SD).

Characteristic	*Nicotine gum (n = 205)*	*Placebo (n = 206)*
Age (years)	45 (10)	44 (10)
Female	65%	59%
Age at onset of daily smoking	17 (5)	16 (4)
Years of smoking	28.0 (9.9)	27.9 (9.0)
Motivation to quit (VAS 0–10)	6.7 (3.0)	6.5 (3.0)
Motivation to reduce (VAS 0–10)	9.3 (1.5)	9.3 (1.9)
Number of cigarettes/day	24 (7)	24 (7)
Carbon monoxide (p.p.m.)	29 (9)	27 (9)
Plasma cotinine (ng/ml)	334 (124)	331 (107)
Plasma thiocyanate (μg/ml)	9.9 (2.7)	10.2 (2.7)
Nicotine dependence (FTND score)	6.4 (1.9)	6.4 (1.8)
Body mass index (kg/m^2)	24.9 (4.3)	25.2 (4.2)

p.p.m. = parts per million; FTND = Fagerström Test of Nicotine Dependence.

Gum usage

Gum use was assessed by asking participants about their average daily consumption of gum. The mean (standard deviation) number of 2 mg and 4 mg nicotine gums used in daily users ($n = 40$ and 78, respectively) was 7.8 (4.3) and 9.8 (5.1) pieces per day, respectively, after 2 weeks. Corresponding figures at

Table 2 Successful smoking reduction and cessation.

Time-point	*Active gum (n = 205)* n *(%)*	*Placebo (n = 206)* n *(%)*	*Odds ratio (95% CI)*	*P value (Fisher's test)*
Reduction (50–100%): sustained from week 6				
Month 4	28 (13.7)	10 (4.9)	3.10 (1.46–6.56)	0.002
Month 12	18 (8.8)	3 (1.5)	6.51 (1.89–22.5)	<0.001
Month 24	13 (6.3)	1 (0.5)	13.9 (1.80–107)	<0.001
Reduction (50–100%): point prevalence				
Month 4	50 (24.4)	21 (10.2)	2.84 (1.64–4.94)	<0.001
Month 12	43 (21.0)	27 (13.1)	1.76 (1.04–2.98)	0.036
Month 24	30 (14.6)	20 (9.7)	1.59 (0.87–2.91)	0.13
Cessation: point prevalence				
Month 4	13 (6.3)	1 (0.5)	13.88 (1.80–107)	<0.001
Month 12	23 (11.2)	8 (3.9)	3.13 (1.36–7.17)	0.005
Month 24	19 (9.3)	7 (3.4)	2.90 (1.19–7.07)	0.015

Table 3 Change in cigarette consumption, carbon monoxide, plasma cotinine and plasma thiocyanate expressed as percentage of baseline for all participants remaining in the study at 4, 12 and 24 months; values are means (SD).

		Cigarettes/day (% of baseline)				*CO (% of baseline)*				*Cotinine (% of baseline)*				*Thiocyanate (% of baseline)*			
Time	*Treatment*	n	*Mean*	*SD*	P*	n	*Mean*	*SD*	P*	n	*Mean*	*SD*	P*	n	*Mean*	*SD*	P*
4 months	Active	122	56	31	0.03	122	71	39	0.01	120	98	36	0.01	120	79	25	<0.001
	Placebo	100	67	25		100	84	33		98	86	25		98	89	18	
12 months	Active	96	46	36	0.05	96	62	42	0.03	95	93	41	0.3	5	75	35	0.01
	Placebo	73	57	31		73	77	39		70	88	39		70	87	25	
24 months	Active	82	54	42	0.2	82	63	42	0.1	81	83	46	0.1	81	74	36	0.2
	Placebo	71	61	34		71	76	42		70	93	46		70	82	27	

**P*-values (Mann–Whitney *U*-test) for comparison between placebo and active groups. Due to missing values there are fewer subjects in the cotinine and thiocyanate analyses.

Table 4 Analysis of biomarkers of cigarette inhalation at 24 months according to outcome groups, i.e. smokers, reducers and abstainers, irrespective of treatment group; values are expressed as means (SD).

	Abstainers[a] *n = 26*	↔	*Reducers = 50%*[b] *n = 25*	↔	*Reducers < 50% = 25%*[c] *n = 35*	↔	*Smokers < 25%*[d] *n = 67*
No. of cigarettes/day	0 (0)	***	5.6 (5.0)	***	13.9 (4.8)	***	20.6 (6.3)
CO (p.p.m.)	3 (2)	***	12 (8)	***	22 (9)	NS	24 (9)
Plasma cotinine (ng/ml)	70 (106)	***	260 (148)	NS	280 (103)	*	327 (116)
Plasma thiocyanate (μg/ml)	3.0 (2.4)	***	6.2 (2.9)	***	8.9 (2.0)	NS	8.6 (2.5)

[a]Point prevalence abstinence = no smoking and CO ≤ 10 p.p.m. at 24 months. [b]Reducers > 50% = subjects reducing smoking ≥ 50% of baseline daily cigarette consumption. [c]Reducers < 50% > 25% = subjects reducing smoking < 50% but ≥ 25% of baseline daily cigarette consumption. [d]Smokers < 25% = subjects reducing <25% including unchanged or increased cigarette consumption. *P*-values (Mann–Whitney *U*-test) for comparison between groups, i.e. a versus b; b versus c; c versus d: ****P* < 0.001; **P* < 0.05.

month 12 were 10.8 (8.3) and 10.6 (5.8) pieces per day ($n = 17$ and 37, respectively).

Compliance was similar in the active and placebo treatment groups. Of 173 subjects, 167 (97%) who attended the 2-week visit in the active treatment group and 150 of 153 (98%) in the placebo group reported use of gum up to that time-point, while at 12 months 64 of 98 (65%) and 35 of 78 (57%) in active and placebo groups, respectively, reported any use of gum.

Changes in attitude to quitting smoking

At the 24-month visit the 153 subjects present and an additional 14 who were contacted by phone were asked: 'Has your participation in the trial changed your attitude towards quitting smoking?' The answers were: 'No, not at all' 31% (51/167); 'Yes, I am more interested in quitting' 67% (112/167); 'Yes, I am less interested in quitting' 1% (1/167); and 'I do not know' 2% (3/167).

Motivation to *quit* smoking decreased for subjects in the active treatment group that had reduced their daily cigarette consumption less than 50% after 24 months. Motivation to *reduce* smoking decreased for unsuccessful reducers in both treatment groups at 24 months (Table 5a,b).

In response to the question: 'How do you intend to change your smoking in the next month?' of the 121 smokers present at the 24-month visit 31 (26%) answered 'quit'; 54 (45%) answered 'reduce from current level' and 36 (30%) answered 'keep current level'.

Adverse events

Subjects in the active treatment group reported 166 adverse events and subjects in the placebo group reported 147 adverse events (NS), with no differences across groups in terms of severity (active gum: 61% mild, 34% moderate and 4% severe). None of the 21 serious adverse events were assessed as related to study treatment. Adverse events relating to possible nicotine overdose (nausea, vomiting and palpitation) were reported by six subjects in the active group and by four in the placebo group. Four subjects stopped treatment prematurely, two in each group.

Table 5 (a) Motivation to reduce smoking for subjects smoking more than 50% of baseline at 12 and 24 months, scored on a visual analogue scale (0–10).

	Baseline			*24 Months*		
	n	*Mean*	*SD*	*Mean*	*SD*	P-*value*[a]
Active	49	9.0	2.3	5.7	3.1	<0.001
Placebo	49	9.3	1.3	6.5	2.9	<0.001

[a]Wilcoxon's signed rank sum test for difference from baseline.

Table 5 (b) Motivation to quit smoking for subjects smoking more than 50% of baseline at 12 and 24 months, scored on a visual analogue scale (0–10).

	Baseline			*24 Months*		
	n	*Mean*	*SD*	*Mean*	*SD*	P-*value*[a]
Active	49	6.5	3.2	4.7	2.8	<0.001
Placebo	49	6.1	2.8	5.2	3.2	0.42

[a]Wilcoxon's signed rank sum test for difference from baseline.

DISCUSSION

Main findings

The main findings from this study are that smoking reduction can be achieved with the aid of nicotine gum treatment and that this reduction promotes smoking cessation. Throughout the study nicotine gum treatment was superior to placebo in achieving smoking reduction and cessation, except for point prevalence reduction at 24 months.

This study suggests that to have one subject reducing cigarette consumption, with at least 50% over 24 months, 17 smokers not ready to quit need to be treated with nicotine gum. The NNT for achieving one smoke-free subject at 24 months is also 17 in these smokers disinclined to quit.

In a minimal intervention smoking reduction study comprising 923 smokers, NRT was compared to placebo and a no-intervention control group (Etter *et al.* 2002). After 6 months the number of daily cigarettes was reduced by 10 in the NRT group, 7.5 in the placebo group and 2.5 in the control group ($P < 0.04$), which is in accordance with the findings in the present paper.

In an earlier clinic-based smoking cessation study using nicotine patches and placebo approximately 7.5% of subjects reduced their smoking by 50% or more after 1 year (Nørregaard *et al.* 1992), which is much lower than in the present study. It would be of interest to investigate if use of the reduction concept for failures in smoking cessation studies could increase success rates.

The most stringent method of reporting outcome in smoking cessation trials is sustained abstinence rate. As the main goal in the present study was smoking reduction, and no target quit day was set, it seemed more appropriate to use point prevalence as cessation outcome measure in this context. A cessation rate of 11% and 4% after 12 months and 9% and 3% after 24 months in active and placebo, respectively, was not expected in this group of smokers who were motivated to reduce smoking but unwilling or unable to quit at baseline. The relative effect of nicotine gum versus placebo was in the same range as that in smoking cessation trials, suggesting that the smoking reduction approach promoted smoking cessation in the present study.

The absolute cessation rate of approximately 10% and NNT of 17 is favourable and underlines that this reduction approach is as cost-effective as 'ordinary' smoking cessation interventions (West, McNeil & Raw 1998) and support the use of NRT to this segment of smokers.

Limitations of the study

A potential limitation of this study is the high premature dropout rate with a 41% 1-year attendance rate. In three other reduction studies the 1-year attendance rate was 40, 44 and 45% (On file, Pharmacia, Helsingborg, Sweden), in contrast to a 83% 1-year attendance rate in a nicotine reduction study with nicotine inhalers (Bolliger *et al.* 2000). As we used intention-to-treat in our outcome analysis, as the only difference between completers and dropouts was a minimal difference in nicotine dependence and age, and as there was no significant difference between dropout for active and placebo, we do not believe that a major bias has occurred due to the high dropout.

To check the robustness of the conclusions obtained under the primary analysis, a second analysis has been performed where missing values have been replaced by estimated values from a linear regression model, with visit as independent variable. The result of this second analysis gave results similar to the primary and gave no reason to change any conclusions being made.

Also, this is supported indirectly by an almost identical 2-year smoking cessation rate in the two studies, i.e. 9.3% in our study versus 10.5% in the Bolliger study for active therapy.

A well-known problem in smoking cessation studies concerns subjects failing to attain follow-up sessions. In a smoking cessation study comprising 3575 smokers with nicotine patches in 17 countries in Europe there was a 1-year attendance rate of 50% and a 25% completion rate (Tønnesen *et al.* 1999).

Participants in the above studies are volunteers not suffering from a disease. Thus, the motivation to continue

in the study if they do not succeed can be expected to decline in most subjects.

In the present study, a higher frequency of initial sessions might have increased retention. Adding a screening visit instead of a brief telephone contact might have resulted in enrolment of more compliant subjects.

Definition of reduction

The definition of reduction used here and in a similar study that used the nicotine inhaler, i.e. 50% or more decrease in daily cigarette consumption, was chosen arbitrarily. With regard to cigarette toxin intake, we observed an approximately linear decline in CO and thiocyanate parallel with the reduction in cigarette consumption but the decrease in toxins was smaller, suggesting that compensatory smoking occurred. Analysis of toxin inhalation suggests that reduction to less than 50% of baseline cigarette consumption results in intake of CO and thiocyanate significantly lower than that in smokers, while less reduction does not significantly alter toxin intake compared to smokers (Table 4). This evidence supports the use of our chosen cut-off value for reduction.

Apart from tobacco exposure markers such as CO and thiocyanate assessed in this study, markers of carcinogenic agents would be of major interest in future studies (Institute of Medicine 2001).

Motivation

We observed a tendency towards a decrease in motivation to reduce or quit in failures during the study period using visual analogue scales at entry and after 2 years. Positive expectations might have led to an overestimation of the motivation to reduce at entry, and the difficulties experienced in achieving reduction may have resulted in lower and more realistic scores during the study. In contrast, motivation to maintain reduction or stay quit increased among successful reducers and abstainers. These findings are supported by two population and one relapse study, where subjects who reduced smoking by more than 50% increased their number of cessation attempts compared to non-reducers, whereas those who reduced by 5–50% did not (Farkas 1999; Hughes, Cummings & Hyland 1999; Etter *et al*. 2002).

CONCLUSION

This study implies that smokers who are not ready to quit could be offered nicotine gum to reduce smoking, as this approach promotes cessation. Smoking reduction decreases the intake of some cigarette toxins, including CO and thiocyanate. The effect of nicotine gum on smoking reduction, including cessation, can be achieved and maintained over a period of 12 months.

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REFERENCES

Benowitz, N. L., Jacob, P., Kozlowski, L. T. & Yu L. (1986) Influence of smoking fewer cigarettes on exposure to tar, nicotine, and carbon monoxide. *New England Journal of Medicine*, **315**, 1310–1313.

Bolliger, C. T., Zellweger, J. P., Danielsson, T., van Biljon, X., Robidou, A., Westin, A., Perruchoud, A. P. & Säwe, U. (2000) Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *British Medical Journal*, **321**, 329–333.

Etter, J. F., Laszlo, E., Zellweger, J. P., Perrot, C. & Perneger, T. V. (2002) Nicotine replacement to reduce cigarette consumption in smokers who are unwilling to quit: a randomised trial. *Journal of Clinical Psychopharmacology*, **22**, 487–495.

Farkas, A. J. (1999) When does cigarette fading increase the likelihood of future cessation? *Annals of Behavior Medicine*, **21**, 71–76.

Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Goldstein, M. G., Gritz, E. R., Heyman, R. B., Jaen, C. R., Kottke, T. E., Lando, H. A., Mecklenburg, R. E., Multen, P. D., Nett, L. M., Robinson, L., Stitzer, M. L., Tommasello, A. C., Villejo, L. & Wewers, E. M. (2000) *Treating Tobacco Use and Dependence.* Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services, Public Health Service.

Hughes, J. R. (2000) Smoking reduction: efficacy and implementation. *Addiction*, **95**, S3–S37.

Hughes, J. R., Cummings, K. M. & Hyland, A. (1999) Ability of smokers to reduce their smoking and its association with future smoking cessation. *Addiction*, **94**, 109–114.

Hurt, R. D., Croghan, G. A., Wolter, T. D., Croghan, I. T., Offord, K. P., Williams, G. M., Djordjevic, M. V., Richie, J. P. Jr & Jeffrey, A. M. (2000) Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine and Tobacco Research*, **2**, 327–336.

Institute of Medicine (IOM) (2001) *Clearing the Smoke: the Science Base for Tobacco Harm Reduction.* Washington, DC: IOM.

Jarvis, M. J., Russell, M. A. & Saloojee, Y. (1980) Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *British Medical Journal*, **281**, 484–485.

Jarvis, M. J., Tunstall-Pedoe, H., Feyerabend, C., Vesey, C. & Saloojee, Y. (1987) Comparison of tests used to distinguish smokers from non-smokers. *American Journal of Public Health*, **77**, 1435–1438.

Jimenez-Ruiz, C., Kunze, M. & Fagerström, K. O. (1998) Nicotine replacement: a new approach to reducing tobacco-related harm. *European Respiratory Journal*, **11**, 473–479.

Lindqvist, R., Lendahls, L., Tollbom, Ö., Åberg, H. & Håkansson, A. (2002) Smoking during pregnancy: comparison of self-reports and cotinine levels in 496 women. *Acta Obstetricia et Gynecologica Scandinavica*, **81**, 240–244.

Nørregaard, J., Tønnesen, P., Simonsen, K., Petersen, L. & Säwe,

U. (1992) Smoking habits in relapsed subjects from a smoking cessation trial after one year. *British Journal of Addiction*, **87**, 1189–1194.

Silagy, C., Lancaster, T., Stead, L., Mant, D. & Fowler, G. (2001) Nicotine replacement therapy for smoking cessation (Cochrane Review). In: *The Cochrane Library*, Issue 3. Oxford: Update Software.

Tønnesen, P., Fryd, V., Hansen, M., Helsted, J., Gunnersen, A. B., Forchammer, H. & Stockner, M. (1988a) Two and four mg nicotine chewing gum and group counselling in smoking cessation: an open, randomised, controlled trial with a 22 month follow-up. *Addictive Behaviors*, **13**, 17–27.

Tønnesen, P., Fryd, V., Hansen, M., Helsted, J., Gunnersen, A. B., Forchammer, H. & Stockner, M. (1988b) Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. *New England Journal of Medicine*, **318**, 15–18.

Tønnesen, P., Paoletti, P., Gustavssson, G., Russell, M. A., Saracci, R., Gulsvik, A., Rijcken, B. & Sawe, U. (1999) Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *European Repiratory Journal*, **13**, 238–246.

Velicer, W. F., Prochaska, J. O., Rossi, J. S. & Snow, M. G. (1992) Assessing the outcome in smoking cessation studies. *Psychological Bulletin*, **111**, 23–41.

West, R., McNeil, A. & Raw, M. (1998) Smoking cessation guidelines and their cost effectiveness. *Thorax*, **53**, S1–S38.

Westley, J. (1987) Thiocyanate and thiosulfate. *Methods in Enzymology*, **143**, 22–25.