

Open randomised trial of intermittent very low energy diet together with nicotine gum for stopping smoking in women who gained weight in previous attempts to quit

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Abstract

Objective To determine whether attempts to prevent weight gain will increase success rates for stopping smoking.

Design 16 week, open, randomised study with 1 year follow up.

Setting Obesity unit.

Subjects 287 female smokers who had quit smoking before but started again because of weight concerns.

Intervention Combination of a standard smoking cessation programme with nicotine gum and a behavioural weight control programme including a very low energy diet. A control group was treated with the identical programme but without the diet.

Main outcome measure Sustained cessation of smoking.

Results After 16 weeks, 68/137 (50%) women had stopped smoking in the diet group versus 53/150 (35%) in the control group ($P=0.01$). Among these women, weight fell by mean 2.1 (95% confidence interval 2.9 to 1.3) kg in the diet group but increased by 1.6 (0.9 to 2.3) kg in the control group ($P<0.001$). After 1 year the success rates in the diet and control groups were 38/137 (28%) and 24/150 (16%) respectively ($P<0.05$), but there was no statistical difference in weight gain.

Conclusions Combining the smoking cessation programme with an intervention to control weight helped women to stop smoking and control weight.

Introduction

A meta-analysis has established that nicotine gum is better than placebo in achieving smoking cessation. Overall success rates, however, remain modest.¹ About 80% of people gain weight after stopping smoking.² Although the mean weight gain has been described as modest, some people gain substantial weight.^{3,4} In some studies,³⁻⁵ but not all,⁶ the weight increase has been greater in women. Women are generally more concerned about weight gain, and this seems to play an important part in relapse to smoking.^{7,8}

Changes in basal metabolic rate,⁹ altered food preferences,¹⁰ or food as a substitute for the psychological effects of tobacco consumption¹¹ might explain the weight increase. The fall in basal metabolic

rate that occurs after stopping smoking cannot be controlled by dietary recommendations, but the other factors could be controlled. However, studies so far have failed to show any benefit of concurrent weight interventions in connection with stopping smoking.^{12,13}

Our obesity unit has developed several programmes that show promising results with weight control in obesity.^{14,15} Intermittent very low energy diets used over a year have had similar results to continuous very low energy diets.¹⁶⁻¹⁸ The Smoking Cessation Clinical Practice Guideline Panel and staff recommended "that smokers not take strong measures to counteract weight gain during a quit attempt."^{19,20} We conducted a randomised trial to determine whether intermittent use of a very low energy diet to improve weight control affected the success of a smoking cessation programme.

Participants and methods

We invited 25 female smokers to focus group discussions to describe their problems with weight control while attempting to stop smoking. These discussions formed the background for the study design.

Treatment programmes

We conducted an open, randomised study of a smoking cessation programme with nicotine gum (Nicorette 2 or 4 mg) and moderate behavioural advice in combination with a behavioural weight control programme and intermittent very low energy diet (Nutrilett 1.76 MJ/day) as total food replacement. The control group followed an identical programme but did not receive the very low energy diet. The study comprised 11 sessions during 16 weeks (weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, and 16). The programme included three group sessions with a dietician and also standardised written information. All sessions (45 minutes) were in groups of 10 to 15 women, with group members all individually randomised to the same treatment. Additional follow up visits were made after 21, 26, 39, and 52 weeks. Participants were offered 2 mg nicotine gum. If their daily consumption exceeded 20 pieces, they could switch to 4 mg. Participants were given free nicotine gum for 3 months and

thereafter recommended to taper consumption, but on request additional nicotine gum was supplied up to 12 months. All participants were recommended a standardised balanced diet of about 6.7 MJ/day. The group meetings were designed as conventional moderate behaviour modification sessions emphasising techniques for stopping smoking and providing support for weight control. The very low energy diet was given free of charge for three, two week periods (weeks 1 and 2, 7 and 8, and 13 and 14). Subjects were recommended not to eat anything else during these periods but to increase their intake of energy free drinks.

Characteristics of participants

Participants were female smokers aged 30 to 60 who wanted to stop smoking and maintain their weight. To be eligible women had to have a body mass index of 23-31, smoke at least 10 cigarettes a day, have smoked for at least three years, and have made at least one serious attempt to stop and restarted because of weight gain. Exclusion criteria were cardiovascular disease in the past 6 months, clinically important renal or hepatic disease, participation in any other clinical study in past 6 months, pregnancy or lactation, lactose intolerance, alcohol or other drug misuse, use of any form of smokeless tobacco or nicotine replacement therapy, gout, acute porphyria, diabetes mellitus type 1, vegetarian diet, or any serious metabolic or malignant disease likely to interfere with compliance. Exclusion criteria were based on safety recommendations for very low energy diets^{16, 20} and nicotine replacement treatment.

Recruitment

An advertisement resulted in 547 responses. A total of 438 women answered a postal questionnaire about admission criteria and brief demographics; 361 were eligible and given a consecutive number in the order their answers were received at the clinic. They were allocated to one of the treatment groups according to the corresponding number in the randomisation list. All women were invited to an information meeting, and they were then divided into groups of 10-15. Seventy four did not attend the clinic so 287 women were finally included in the study. As this dropout was expected, the protocol defined the intention to treat analysis to comprise women coming to the first visit and receiving treatment.

Data collection, power calculation, and statistics

Based on results from previous studies¹ and the fact that weight conscious women would be a difficult group, we expected about 20% of women in the control group and 35% in the diet group successfully to stop smoking after 16 weeks. Given these assumptions, a sample size of 135 women in each arm of treatment was needed for a power of 80% and an α of 0.05.

No formal adjustment for multiplicity was made, but P values are presented for each test. We used Pearson's χ^2 test for unordered categorical or binary variables and the Mann-Whitney U test for ordered categorical and all continuous variables.

Successful smoking cessation was defined as self reported complete abstinence from week 2 to week 16,

verified by a carbon monoxide concentration less than 10 ppm (New Smokerlyzer, Bedfont). Two missed visits between weeks 2 and 16 were allowed. If the week 2 visit was missing, the woman had to be abstinent from week 1 until endpoint. Women had to attend the week 16 visit to be eligible for the success criteria.

Compliance with the very low energy diet was based on self reported adherence and verified through ketone body analysis in urine, sampled by the women at home. Women with missing samples were asked to provide a urine sample after the very low energy diet period. Compliance with nicotine gum treatment was based on self reported daily number of gums and verified by saliva cotinine concentration.²¹

Withdrawal symptoms,²² including desire or urge to smoke; irritability, frustration, or anger; restlessness; difficulty concentrating; anxiety; dysphoric or depressed mood; insomnia; and increased appetite, together with six fasting related symptoms (headache, constipation, fatigue, nausea, hair loss, and chilliness)²⁰ and adverse events were recorded at each visit.

The study was performed according to the principles outlined in the Declaration of Helsinki and approved by the ethics committee at the Karolinska Hospital. All participants gave informed consent.

Results

Table 1 shows the characteristics of the participants. Mean number of daily cigarettes smoked was 19.5 (95% confidence interval 18.8 to 20.2) for 28.8 (27.9 to 29.6) years. Subjects were moderately nicotine dependent. Almost three quarters (210) of the women had used nicotine replacement therapy before, and 199 (70%) had tried to stop smoking three times or more. In all, 206 (72%) had gained 3-10 kg and 56 (19%) more than 10 kg last time they tried to quit. Two thirds had tried to lose weight during a previous attempt to stop smoking.

Table 1 Baseline demographic characteristics including smoking status and smoking history. Values are mean (SD) unless stated otherwise

	Very low energy diet (n=137)	Control (n=150)
Age (years)	46.9 (7.0)	46.8 (6.9)
Height (cm)	166 (6.0)	167 (6.2)
Body mass index	26.7 (2.2)	26.9 (2.3)
Blood pressure (mm Hg)	125/80 (18/11)	128/81 (18/11)
Heart rate (beats/min)	77 (9.3)	76 (9.4)
Waist:hip ratio	0.82 (0.06)	0.82 (0.06)
Age started smoking (years)	16.1 (3.0)	16.5 (3.3)
Years smoked	29.6 (6.9)	28.1 (7.4)
Cigarettes smoked/day	20.0 (6.3)	19.1 (6.2)
Expired carbon monoxide (ppm)	18.6 (9.1)	18.2 (7.9)
Saliva cotinine (ng/ml)	303.3 (145.5)	269.9 (124.9)
Fagerström tolerance questionnaire	5.9 (2.2)	5.8 (1.8)
No (%) tried to quit smoking \geq 3 times	98 (72)	101 (68)
No (%) used nicotine replacement therapy before	105 (77)	105 (70)
Nicotine gum	83 (61)	76 (51)
Nicotine patch	68 (50)	68 (45)
No (%) with another smoker in household	36 (26)	44 (29)
No (%) quite or extremely sure of succeeding this time	106 (77)	110 (74)
No (%) gained 3-10 kg last time tried to quit	95 (69)	111 (74)
No (%) gained >10 kg last time tried to quit	27 (20)	29 (19)
No (%) tried to lose weight before	129 (94)	147 (98)
No (%) tried to lose weight while stopping smoking	83 (61)	110 (74)

Table 2 Number of women who had completely and continuously stopped smoking from week 2 onwards

Week	No (%) on very low energy diet (n=137)	No (%) of controls (n=150)	% difference (95% CI)	P value*
2	116 (85)	98 (65)	20 (9.6 to 29.1)	0.0002
4	94 (69)	76 (51)	18 (6.8 to 29.1)	0.002
6	84 (61)	70 (47)	14 (3.2 to 26.1)	0.012
8	80 (58)	61 (41)	17 (6.3 to 29.1)	0.003
10	72 (53)	56 (37)	16 (3.8 to 26.6)	0.010
12	71 (52)	60 (40)	12 (0.36 to 23.3)	0.045
14	67 (49)	51 (34)	15 (3.6 to 26.2)	0.010
16	68 (50)	53 (35)	15 (3.0 to 25.6)	0.014
52	38 (28)	24 (16)	12 (2.2 to 21.3)	0.016

*Pearson's χ^2 test.

The smoking cessation rate in the diet group was 68/137 (50%) after 16 weeks compared with 53/150 (35%) in the control group (P=0.01; table 2). The slight increase in success rate from week 10 to 12 in the control group and 14 to 16 in both groups is probably due to women being allowed to miss up to two visits without disqualification from the analysis.

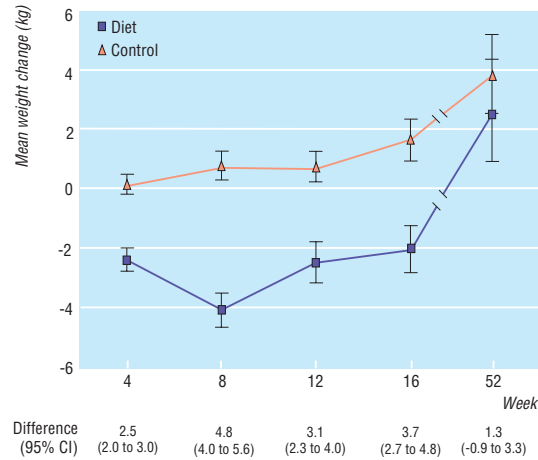


Fig 1 Mean weight change from baseline in women who had completely and continuously stopped smoking. Very low energy diet was used in weeks 0 to 2, 6 to 8, and 12 to 14. Bars represent 95% confidence intervals

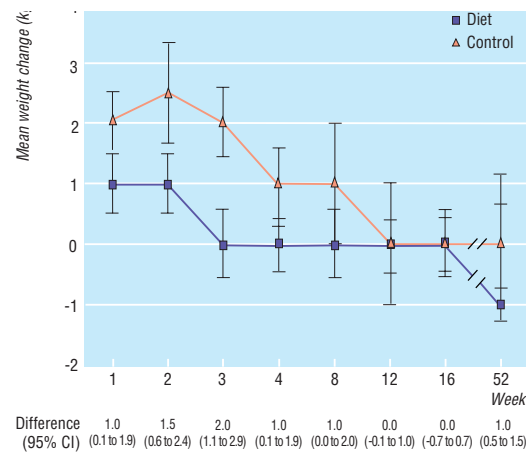


Fig 2 Median change in mood score from baseline during first 4 weeks in continuously abstinent women. Bars represent 95% confidence intervals

Figure 1 shows the mean weight change in women who had successfully stopped smoking. The diet group had lost 2.1 (2.9 to 1.3) kg at 16 weeks whereas the control group had gained 1.6 (0.9 to 2.3) kg (P<0.001). No body mass index dropped below 20.

Mood items in the withdrawal symptoms questionnaire (irritability, anxiety, poor concentration, restlessness and depression; score 0-15)^{22, 23} were analysed in continuous abstainers up to week 16. The diet group reached the highest score after 1 week whereas the control group peaked after 2 weeks, when the difference between the group medians was 1.5 units (0.6 to 2.4). The score of the diet group was significantly lower than that of the control group at weeks 2, 3, and 4 (fig 2).

Adverse events

Rhinitis and headache were the most common adverse events, reported by 170 (59%) and 105 (37%) women during the study. No significant differences were found between the groups, although headache was reported by 58 (42%) women in the diet group and 47 (31%) in the control group (P=0.053, 95% confidence interval for difference -0.1 to 22.1). Eighty six women withdrew from treatment during the 12 months. None of the withdrawals were because of adverse events.

Long term success

After 12 months, 35 and 51 women had dropped out from the diet and control groups respectively. Thirty eight (28%) of the diet group were still not smoking compared with 24 (16%) in the control group (P=0.02). Among non-smokers, the mean weight increase was 2.5 (0.78 to 4.3) kg in the diet group and 3.8 (2.5 to 5.1) kg in the control group (P=0.61). The overall weight increase irrespective of smoking status was 1.2 (0.32 to 2.1) kg in the diet group and 2.3 (1.5 to 3.0) kg in the control group (P=0.13).

Compliance

Women who successfully stopped smoking in the diet group used 7.8 gums/day and those in the control group used 8.3/day during the first 16 weeks. Fifteen subjects used 20 or more gums a day and switched to 4 mg gum. Ninety six of the women who came to the clinic after one year (n=201) were still using the gum. Ninety four used 5.4 (SD 4.1) 2 mg gums/day and two women used 7.0 4 mg gums/day.

In all, 103/137 (75%) women reported total compliance with the very low energy diet during the

first period. During weeks 6 to 8 and 12 to 14 complete compliance was reported by 42 (31%) and 25 (18%) respectively. These figures were confirmed by the ketone body analysis.

Discussion

Our study shows that smoking can be stopped for up to one year with acceptable weight control in a group of women selected for their previous weight control problems when attempting to stop smoking. This study was open, and all subjects received nicotine replacement therapy. There is no practical way to blind very low energy diets, and there is ample evidence that nicotine replacement improves abstinence from smoking.²⁴

It is reasonable to assume that programmes to stop smoking have lower success in weight conscious women than in the general smoking population. Generally, the success rate after 12 months is 19%,²⁴ compared with our results of 28% in the diet group and 16% in controls. Women were given the opportunity to drop out of the treatment programme between randomisation and the first visit, and this probably resulted in a more motivated study population.

Role of very low energy diets

While on the very low energy diet women experienced less craving for cigarettes and increased appetite scores. This may reflect diet induced acidosis, as ascertained by measurement of urinary ketone bodies. Although clinical experience suggests that weight loss is facilitated by acidosis, which is associated with fat catabolism, no clear proof exists.

Very low energy diets have not been previously reported in programmes to stop smoking. Weight gain when stopping smoking has, however, been prevented by giving an anorectic drug,²⁵ but when drug treatment was discontinued, weight was regained almost up to the control group level.

Safety

Combining smoking cessation and weight control produced only modest side effects. Headache was more common in the diet group (although not significantly), and this can partly be explained by the fact that headache is a common side effect both of nicotine withdrawal²² and supplemented fasting.²⁶ As expected, compliance with the very low energy diet fell over time.¹⁶ However, the immediate differences in stopping smoking between the two groups were already evident after 2 weeks. Thus the first diet period may be the critical phase. Focusing on weight, in an obesity unit, probably helped the women stop smoking by providing more weight control information than they had previously received.

Our study was designed with power to determine smoking cessation rates and weight change up to week 16. Although significantly improved smoking cessation rates were found after one year in the diet group, the study did not have power to demonstrate significant differences in weight gain between the groups. The weight gain in both groups was less than reported by most women in previous attempts at stopping smoking. Nicotine gum may therefore depress and postpone weight gain.

Contributors: TD designed the trial, interpreted the results, and prepared the manuscript. SR was principal investigator and responsible for clinical conduct, interpreted results, and wrote the manuscript. ÅW performed the statistical analyses. Urbain Sæwe initiated the trial and contributed with ideas and valuable professional input. Nurses and dieticians at the obesity unit at Karolinska and Huddinge Hospitals collected all study data.

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Commentary: results are unlikely to be as good in routine practice

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General practitioners and primary care physicians of all types are used to being harangued about the issue of stopping smoking. Although stopping smoking is probably the largest beneficial health decision any smoker can make, it is important to determine how far each individual patient should be pushed on this issue. It is part of health promotion folklore that 5% of smokers will stop merely on the advice of their general practitioner; the use of nicotine replacement therapy increases the proportion of successful quitters.

Danielsson et al have provided a well conducted study which suggests that the use of very low energy diets together with nicotine gum boosts one year cessation rates from 16% to 28%. On the face of it, this is a dramatic and meaningful increase that deserves to be considered in routine practice. However, a number of factors must be reflected on before this initiative is taken up more widely. The first of these concerns the nature of the sample of patients in this study. The women entered were all in the normal or overweight category, wanted to stop, and had failed to stop before because of unacceptable weight gain. Careful patient

selection would be necessary before entering subjects routinely into this programme.

Secondly, in the research setting about a fifth of those enrolled did not turn up for the sessions—in service use this proportion could easily be greater. Thirdly, the intensity of the behavioural programme must be remembered. Eleven, 45 minute group sessions (10-15 women each) were held over 16 weeks. This level of intervention is not only expensive but nearly impossible to provide in routine practice. Furthermore, the very low energy diet was provided free for the participants in this research. This would be unlikely outside the research setting.

Although the study was done well, it did not include any data on cost effectiveness. It would have been interesting to know a cost per successful quitter. Readers of this paper might be tempted to try a version of the method for their own patients, probably using the diet alone without the group sessions. It is unlikely that results would come near those achieved in the research setting, and thus the case for dietary restriction as an adjunct to nicotine replacement therapy when stopping smoking remains unproved for the moment.

When I use a word . . .

Now concentrate

Dictionaries were originally selective glossaries, often of so called "hard words." Nowadays, however, we expect them to be comprehensive, from a to zyzzygoton. Nevertheless, occasionally even an established word is omitted. For instance, "liar" was mistakenly omitted from the 1972 edition of *Chambers Twentieth Century Dictionary* and "bondmaid" from the fascicle in the *Oxford English Dictionary* for which it had been prepared (Battellie-Bozzom, 1887). I have also read that James Murray omitted "appendicitis" from the first edition of the *OED* on the advice of Sir William Osler, then regius professor of medicine at Oxford, who said that it was medical jargon that wouldn't last; the word gained currency when, just before he was due to be crowned in 1902, King Edward VII, already on the throne, fell ill and had his inflamed appendix removed by Frederick Treves.

"Concentration" is defined in the *Dent Dictionary of Measurement* (J M Dent, 1994) as "The amount of a particular substance in a mixture or solution." Now, excellent though it is, I would not normally quote a definition from Dent's dictionary. I have done so here because it is missing from the *OED*.

Of course, "concentration" is a headword in the *OED*, but none of its seven main definitions is the meaning defined above. When I drew this to the attention of John Simpson, one of the current editors of the *OED*, he agreed that the dictionary had lapsed and he opened a file. However, such is the richness of the *OED* that entries under other headwords contain quotations that illustrate the use of the word.

Making a quick search of the whole text on CD Rom, I unearthed "concentration" in the sense given above in many quotations under other headwords. The earliest examples are, as it were, concentrated in the years 1897-9, surprisingly late, given the great advances that occurred in the science of chemistry during the nineteenth century. For example, "It is the difference in the concentration of the chemotropic substance in two layers . . . which controls movement" (*Am Naturalist* 1897;31:719).

In earlier examples than this it is often hard to distinguish between this meaning of concentration and its parent meaning, "the strengthening of a solution by contraction of its volume."

"Level" in the sense of "concentration" is also not defined as such in the *OED*, but again examples of its use in this way can be found under other headwords. For example, under "para-": "The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium" (*J Biol Chem* 1925; 63:395).

"Level" in this sense is now used more often than "concentration." In 118 056 papers published in the bioscience literature in 1965-97 "level" was used in 54.4% of cases. However, this average figure conceals an unusual phenomenon: "blood level" was used markedly more often than "blood concentration" (68.5% vs 31.5%) while "plasma level" was used less often than "plasma concentration" (48.5% vs 51.5%). More research might show why, but for the moment I cannot offer a good explanation for this difference.

Using "level" to mean "concentration" may be colloquial, but it is hardly scientific. This is a matter that is best contemplated at leisure in the bath, where you have time to consider the difference between the level of water in the tub and the concentration of bathsalts in the water.

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We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.