19 Swedish cases reported in 1987-8 to the calculated number of new prescriptions of angiotensin converting enzyme inhibitors in Sweden during this period. By extrapolating data from the Jämtland study and the prescription survey,[20] the number of new prescriptions can be roughly estimated as 117 200. Thus, a risk of one report for every 6200 new prescriptions can be calculated. This estimate is very rough, however, since both the numerator (actual reporting rate unknown) and the denominator (extrapolation from random samples) are associated with a considerable uncertainty.

CONCLUSION

Symptoms of airway obstruction caused by angiotensin converting enzyme inhibitors seem to be rare, but doctors should be aware of these reactions. Asthmatic patients may be more susceptible than others. Any suspicion of bronchospasm or aggravated asthma, even with patients who cough, should be carefully monitored and documented. Such adverse reactions usually require discontinuation of the angiotensin converting enzyme inhibitor.

The conclusions reached in this paper reflect the judgment of the authors and do not represent the opinion of the WHO.

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How effective is nicotine replacement therapy in helping people to stop smoking?

Jin Ling Tang, Malcolm Law, Nicholas Wald

Abstract

***Objective*—To assess the efficacy of nicotine replacement therapy in helping people to stop smoking.**

***Design*—Analysis of the results of 28 randomised trials of nicotine 2 mg chewing gum, six trials of nicotine 4 mg chewing gum, and six trials of nicotine transdermal patch.**

***Subjects and setting*—Subjects were self referred (responding to advertisements or attending anti-smoking clinics) in 20 trials and invited (general practice or hospital patients) in 20. Therapists in self referred trials were generally experienced in helping people stop smoking but not in invited trials.**

***Main outcome measure*—Efficacy was defined as difference in percentages of treated and control subjects who had stopped smoking at one year.**

***Results*—Efficacy was highly significant ($P < 0{\cdot}001$) for both gum and patch. Nicotine 2 mg chewing gum had an overall efficacy of 6% (95% confidence interval 4% to 8%), greater in self referred subjects than in invited subjects (11% *v* 3%). Efficacy depended on the extent of dependence on nicotine as assessed by a simple questionnaire; it was 16% (7% to 25%) in "high dependence" smokers, but in "low dependence" smokers there was no significant effect. The 4 mg gum was effective in about one third of "high dependence" smokers. The efficacy of the nicotine patch (9% (6% to 13%) overall) was less strongly related to nicotine dependence, perhaps because the patch cannot deliver a bolus of nicotine to satisfy craving.**

***Conclusions*—Both gum and patch are effective aids to help nicotine dependent smokers who seek help in stopping. Among the most highly nicotine dependent smokers (those craving a cigarette on waking) the 4 mg gum is the most effective form of replacement therapy; it could enable one third to stop. In less highly dependent smokers the different preparations are comparable in their efficacy but the patch offers greater convenience and minimal need for instruction in its use. Overall, nicotine replacement therapy could enable about 15% of smokers who seek help in stopping smoking to give up the habit.**

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Introduction

Various forms of nicotine replacement therapy have been used to help people stop smoking. We report here a systematic analysis of the randomised controlled trials of nicotine replacement therapy,[1-39] with the objective of determining its efficacy and the circumstances in which it is most effective.

NICOTINE REPLACEMENT PREPARATIONS

Nicotine taken orally may produce indigestion and other side effects and is largely metabolised in the liver before reaching the systemic circulation. Direct absorption into the systemic circulation through the

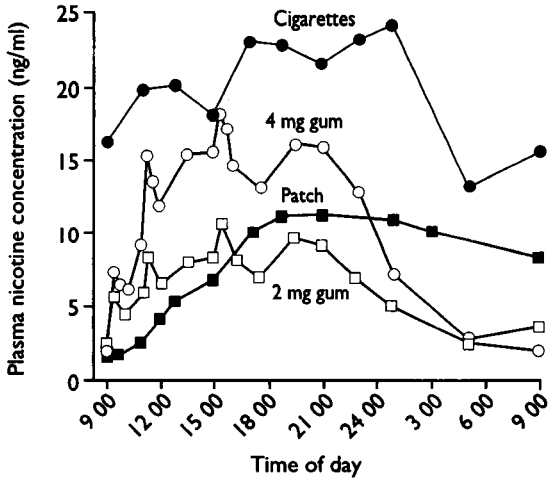
buccal or nasal mucosa, the alveoli, or the skin can, however, produce sufficient concentrations of nicotine in blood to partially allay withdrawal symptoms.

Nicotine chewing gum (Nicorette) is marketed in 2 mg and 4 mg strengths. The nicotine is attached in a loose bond with the ionic bonding agent polacrilex, and intermittent chewing releases about 90% of the available nicotine after 20 minutes.[40] Most is absorbed through the buccal mucosa; on average about a quarter is swallowed in saliva and metabolised but there is much variation between individuals.[41] Correct chewing technique is important—many people chew the gum too quickly. Gradual withdrawal after three months' use is recommended. The 2 mg gum can be bought over the counter in Britain; the 4 mg gum is available only on prescription.

Nicotine skin patches release nicotine into the blood at a slow constant rate. Three brands are licensed in Britain and available over the counter. Two (Nicotinell and Nicabate) are worn constantly for 24 hours, with three strengths corresponding to patch areas of 30, 20, and 10 cm^2, delivering 21, 14, and 7 mg of nicotine into the circulation over 24 hours. One (Nicorette) is a 16 hour patch, removed at night, with three strengths; 15 mg, 10 mg, and 5 mg. Courses of about three months are recommended, beginning with a higher dose patch and reducing at intervals.

The figure shows data from Benowitz and colleagues on typical plasma nicotine concentrations produced by smoking and by using replacement therapy.[41-43] (Data from Russell and colleagues are similar.[44,45]) Steady state nicotine concentrations are higher with 4 mg gum than with 2 mg gum or the patch, but no form of replacement therapy achieves levels as high as those from smoking 20 cigarettes a day. The rate of increase to steady state concentrations is slow with the patch. With the 16 hour patch this slow increase must be repeated every morning; the 24 hour patch maintains constant plasma concentrations of about 10 ng/ml, which at night are comparatively high. The immediate effect of smoking is poorly reproduced by replacement therapy. One cigarette produces a rapid "surge" of plasma nicotine; the level rises by about 25 ng/ml within minutes but rapidly declines.[41,44,45] Nicotine gum produces a smaller rise over 30 minutes,[45] and the patch produces no immediate effect.

Nicotine nasal spray (not yet commercially available) is absorbed through the nasal mucosa. It might satisfy craving more effectively as it produces a steady state plasma nicotine concentration similar to that from smoking and delivers a rapid surge of plasma nicotine, over half that attained from smoking a cigarette.[38,45] A



Plasma concentrations of nicotine over a 24 hour period in subjects smoking cigarettes ad libitum (22 day on average, n=8), using 2 mg gum (n=7) and 4 mg gum (n=7) hourly from 9 am to 9 pm, and using 21 mg transdermal patch for 24 hours (n=11). Data from Benowitz et al[41-43]

Subjects in randomised trials of nicotine replacement therapy

Self referred subjects—with specialist assistance

Community volunteers—healthy smokers recruited through advertising to attend specialist clinics

Antismoking clinics—subjects already attending antismoking clinics. Most had tried other means of stopping smoking; some had diseases related to smoking

Invited subjects with non-specialist assistance

General practice—all available smokers were non-selectively invited by a doctor to participate in the trial. Most of these trials recruited people attending their general practitioner for a minor illnesss; a few were in occupational settings. There was often little instruction and encouragement in the appropriate use of the nicotine gum

Hospital—patients were non-selectively invited by a doctor to participate. Many of the patients had diseases related to smoking

nicotine inhaler has been tested; the nicotine is absorbed through the alveoli as with cigarette smoking, but plasma nicotine levels are lower than with the nasal spray.[39] Various unlicensed products are sold in Britain. Nicotine lozenges and tablets (to be sucked in the mouth) have low nicotine content (0·4-1·1 mg), but frequent use can produce high blood nicotine levels,[46] similar to 4 mg gum. Their efficacy in helping people stop smoking has not been tested in trials.

Methods

The randomised trials of nicotine replacement therapy were identified by using Medline and *Index Medicus*, by scrutiny of the citations of review articles and of each trial, and by consultation with experts in the field. The trials fell into two broad categories, self referred subjects and invited subjects (box). The self referred subjects were likely to be more highly motivated, but the trials do not permit distinction between the effects of subject motivation and experience of the therapist.

DATA ANALYSIS

We defined efficacy as the difference between the percentages of treated and control subjects who had stopped smoking at one year. (Use of the ratio of the two, a relative rate, yielded similar conclusions.) In all trials treated and control subjects who did not complete the trial were assumed not to have given up smoking.

We used as the outcome measure the point prevalence of smoking cessation at one year in preference to sustained cessation over a period because in most of the trials the point prevalence was verified by measuring biological markers of tobacco smoke intake at one year. Point prevalence was not available for four trials,[7,19,25,37] but the difference in the two outcome measures was small. The main biological marker was carbon monoxide; cotinine or nicotine were not used as they would detect use of replacement therapy. In these trials, measurements of biological markers in 5-25% of subjects who claimed to have stopped smoking indicated that the subjects were still smoking, but the proportion of such subjects was similar in treated and control groups. In trials without such measurements it is therefore reasonable to assume that the difference in the rate of giving up between treated and control groups is not biased.

For seven of the gum trials and two of the patch trials the cessation rates were available only at six months. These were included because in trials of 2 mg gum that published cessation rates at both six and 12 months the

difference between treated and control groups remained constant (9%).[5 9 11 13 15 21 26] Efficacy was also similar at 24 months.[26 29 30] Trials with shorter follow up than six months were not included.

The estimates of efficacy from different trials were combined by using the method of DerSimonian and Laird.[47] Results from different trials were stratified according to the trial setting (self referred or invited subjects as described above). Subgroup analyses were done in trials that measured the degree of nicotine dependence in subjects (dependent smokers should be more likely to respond to replacement therapy). A simple questionnaire, the Fagerström tolerance questionnaire,[48 49] (see appendix) classified smokers into two groups with "high" (seven or more points out of 11, about a third of smokers[15 26 50]) and "low" degrees of nicotine dependence.

TABLE I—*Results of randomised trials of 2 mg nicotine chewing gum versus control*

Trial (first author)	Gum group: No of subjects	Gum group: No (%) who quit	Control group: No of subjects	Control group: No (%) who quit	Difference (%)
Self referred subjects, specialist therapists					
Community volunteers:					
Malcolm[1]	73	17 (23)	63	5 (8)	15
Jarvik[2]	25	7 (28)	23	4 (17)	11
Killen[3]	22	11 (50)	20	6 (30)	20
Clavel[4]	205	24 (12)	222	6 (3)	9
Hall[5]	71	30 (42)	68	14 (21)	21
Areechon[6]	99	56 (57)	101	37 (37)	20
Hughes[7]	20	8 (40)	39	7 (18)	22
Killen[8]	600	127 (21)	618	106 (17)	4
Pirie[9]	206	75 (36)	211	50 (24)	13
Antismoking clinics:					
Jarvis[10]	58	27 (47)	58	12 (21)	26
Fee[11]	180	23 (13)	172	15 (9)	4
Fagerström[12]	50	30 (60)	50	22 (44)	16
Hjalmarson[13]	106	29 (27)	100	16 (16)	11
Invited subjects, non-specialist therapists					
General practice:					
Russell[14]	679	110 (16)	675	73 (11)	5
Fagerström[15]	96	28 (29)	49	5 (10)	19
Jamrozik[16]	100	10 (10)	97	8 (8)	2
Page[16a]	114	8 (7)	93	9 (10)	-3
Campbell[17]	424	19 (5)	412	11 (3)	2
Sutton[18]	270	21 (8)	64	1 (2)	6
Sutton[19]	79	8 (10)	82	2 (2)	8
Gilbert[20]	112	12 (11)	111	9 (8)	2
Hughes[21]	210	35 (17)	105	15 (14)	3
Ockene[22]	402	66 (16)	420	48 (11)	5
Segnan[23]	294	22 (8)	275	15 (5)	2
Harackiewicz[24]	99	12 (12)	52	7 (13)	-1
Hospital:					
British Thoracic Society[25]	410	56 (14)	813	105 (13)	1
Tønnensen[26]	60	23 (38)	53	12 (23)	16
Jensen[27]	211	49 (23)	285	65 (23)	0

TABLE II—*Summary estimates of efficacy* in 28 trials of 2 mg nicotine chewing gum*

Category of trial	No of trials	No of subjects	Pooled estimate of efficacy* (95% confidence interval)
Self referred subjects	13	3460	11% (7% to 15%)
Community volunteers	9	2686	11% (7% to 16%)
Antismoking clinics	4	774	12% (3% to 21%)
Invited subjects	15	7146	3% (2% to 5%)
General practice	12	5314	4% (2% to 6%)
Hospital	3	1832	2% (-3% to 7%)
All trials		10 606	6% (4% to 8%)

*Difference in cessation rate between treated and control subjects.

TABLE III—*Subgroup analyses according to nicotine dependence in six trials of 2 mg nicotine chewing gum*

Trial (first author)	Gum group: No of subjects	Gum group: No (%) who quit	Control group: No of subjects	Control group: No (%) who quit	Difference (%)
High dependence					
Self referred					
Jarvik[2]	17	7 (41)	13	1 (8)	33
Areechon[6]	46	29 (63)	113	43 (38)	25
Fagerström[12]	27	15 (56)	29	9 (31)	25
Overall difference (95% confidence interval)					27% (14% to 39%)
Invited:					
Fagerström[15]	49	13 (27)	18	1 (6)	21
Hughes[21]	52	10 (19)	29	4 (14)	5
Jensen[27]	109	30 (28)	133	28 (21)	6
Overall difference (95% confidence interval)					10% (1% to 19%)
Difference in all trials (95% confidence interval)					16% (7% to 25%)
Low dependence					
Self referred:					
Jarvik[2]	8	0 (0)	10	3 (30)	-30
Areechon[6]	33	17 (52)	8	4 (50)	2
Fagerström[12]	20	15 (75)	20	13 (65)	10
Overall difference (95% confidence interval)					0% (-19% to 19%)
Invited:					
Fagerström[15]	46	15 (33)	30	4 (13)	19
Hughes[21]	126	21 (20)	61	10 (20)	0
Jensen[27]	86	19 (22)	138	37 (27)	-5
Overall difference (95% confidence interval)					3% (-9% to 15%)
Difference in all trials (95% confidence interval)					2% (-7% to 10%)

Results

NICOTINE CHEWING GUM (2 MG)

Table I shows the individual results of the 28 randomised controlled trials of 2 mg nicotine chewing gum versus control (either placebo gum or no gum). The overall estimate of efficacy (the difference in cessation rates between treated and control groups) was 6% (95% confidence interval 4% to 8%; $P<0.001$). Table II shows the summary estimates of efficacy for the different categories of trials. The pooled estimate from trials of self referred subjects, 11% (7% to 15%), was greater than for invited subjects, 3% (2% to 5%) ($P<0.001$). This division largely accounted for the highly significant heterogeneity between the results of all 28 trials ($\chi^2_{26}=57$, $P=0.001$); there was less heterogeneity among the 13 trials of self referred subjects ($\chi^2_{12}=21$, $P=0.06$) and among the 14 trials of invited subjects ($\chi^2_{14}=20$, $P=0.12$).

The analysis of six trials in which the nicotine dependence of smokers was measured by the Fagerström questionnaire or a similar questionnaire showed that nicotine dependence was an important determinant of efficacy (table III). The overall estimate of efficacy in high dependence subjects was 16% ($P=0.004$); the estimate of 2% in low dependence subjects was not statistically significant. The difference in efficacy between smokers with high and low dependence was 14% ($P=0.02$) overall, but was more pronounced (27%, $P=0.02$) in self referred subjects.

The most common side effects were hiccups, flatulence, indigestion, and nausea (each was significantly more common in treated subjects by 7-10%[6 8 10 11 13 24]). These adverse effects were seldom severe enough to stop the use of the gum and could be avoided by learning appropriate chewing techniques and not swallowing air or saliva. Jaw ache from chewing affected about a fifth of subjects using both nicotine and placebo gum. Users also commented on the unpleasant taste of the gum.

Few trials reported data on long term dependence in users of nicotine gum. In an observational study 34 (6%) of 538 patients at an antismoking clinic were still using the gum after one year, representing 25% of all abstainers.[51] Similar one year estimates were reported in two of the trials; half as many subjects were still using the gum at two years.[13 26]

NICOTINE CHEWING GUM (4 MG)

Table IV shows the results of six randomised trials that compared 4 mg nicotine chewing gum with 2 mg gum or placebo gum, or both. The questionnaire on nicotine dependence was given in four of the trials; these showed that in high dependence smokers the 4 mg gum was superior to 2 mg gum ($P<0.001$). The overall difference in the percentage of subjects stopping smoking between users of 4 mg and 2 mg gum was 21% (9% to 32%). In one trial comparing 4 mg gum with placebo[30] the point estimate of efficacy among high dependence smokers was 35% (table IV). This result is supported by the similar estimate of 37% derived by adding the estimates of 21% for 4 mg gum *v* 2 mg gum and 16% for 2 mg gum *v* no gum (table III). Overall, the 4 mg gum enabled about a third of high

TABLE IV—*Results of trials using 4 mg nicotine chewing gum with subjects categorised according to nicotine dependence*

Trial (first author)	4 mg Gum		2 mg Gum		Placebo gum		% Difference (95% confidence interval)	
	No of subjects	No (%) who quit	No of subjects	No (%) who quit	No of subjects	No (%) who quit	4 mg *v* 2 mg	4 mg *v* 0
High dependence:								
Kornitzer[28] (self referred)	73	24 (33)	86	16 (19)			14	
Tønnesen[26] (invited)	27	12 (44)	33	4 (12)			32 } 21 (9 to 32)	
Tønnesen[29] (invited)	15	7 (46)	21	4 (19)			28	
Blöndal[30] (self referred)	44	17 (39)						35 (12 to 58)
Low dependence:								
Kornitzer[28] (self referred)	17	5 (29)	8	5 (63)			−33	
Tønnesen[29] (invited)	36	9 (25)	39	15 (38)			−13 } −18 (−36 to 1)	
Low dependence:								
Blöndal[30] (self referred)	48	20 (42)			62	23 (37)		5 (−13 to 23)
Dependence not assessed:								
Hughes[7] (self referred)	19	5 (26)	20	8 (40)	39	7 (18)	−14	8
Puska[31] (self referred)	116	29 (25)			113	21 (19)		6

TABLE V—*Results of randomised trials of transdermal nicotine patch in smoking cessation*

Trial (first author)	Nicotine dose	Duration of use per day (hours)	Nicotine patch		Placebo		% Difference	Summary difference
			No of subjects	No (%) who quit	No of subjects	No (%) who quit		
Self referred subjects:								
Daughton[32]	21 mg	24	51	11 (22)	52	4 (8)	14	
	21 mg	16	55	17 (31)			23	
Transdermal Nicotine Study Groups[33]	21 mg	24	249	65 (26)	253	31 (12)	14	12% (8% to 16%)
	14 mg	24	254	46 (18)			6	
Tønnesen[34]	15 mg	16	145	25 (17)	144	6 (4)	13	
Invited:								
Müller[35,36]	21/14 mg*	24	100	17 (17)	99	11 (11)	6	
Müller[35]	21/14 mg*	24	56	10 (18)	56	6 (11)	7	6% (2% to 10%)
Russell[37]	15/10 mg	16	400	50 (13)	200	13 (7)	6	
All trials								9% (6% to 13%)

*Those smoking > 20 cigarettes a day used 21 mg patches; those smoking < 20 used 14 mg patches.

dependence smokers to stop smoking. In low dependence smokers, however, there was no evidence that the 4 mg gum was better than 2 mg gum (which itself has little or no effect; table III). Indeed the point estimate, though not statistically significant, suggests that using 4 mg gum reduced the chance of success in low dependence smokers: possibly they were discouraged as the taste of the 4 mg gum is more unpleasant than that of the 2 mg gum, and in one trial[29] side effects (mostly relating to inappropriate chewing technique) were more common.

NICOTINE SKIN PATCHES

Table V shows the results of six randomised trials that compared nicotine transdermal patch with placebo patch. The overall estimate of efficacy was 9% (6% to 13%, $P < 0.001$). The efficacy in self referred subjects, 12% (8% to 16%), was again significantly greater than that in invited subjects, 6% (2% to 10%) ($P = 0.04$). Other published trials comparing nicotine patch with placebo[52,53] (not analysed here because their follow up was shorter than six months) had early results similar to the six trials included in this analysis. Direct randomised comparison of the 21 mg and the 14 mg transdermal patch showed that the 21 mg patch was the more effective ($P = 0.03$, table V).[33] While there has been no direct comparison, the pooled estimates from the trials of patches and of 2 mg gum suggest that the two treatments are of similar efficacy (tables II, V).

Efficacy of the nicotine patch was less strongly related to nicotine dependence than that of the gum. There is evidence that efficacy increases with level of dependence,[36] but at the highest level of dependence (Fagerström score of 9 or above[36] or self reported craving for a cigarette within five minutes of waking[37]) the patch had little effect. Long term dependence on the nicotine skin patch was not reported. Nicotine skin patches often caused mild local skin reactions in people with normal skin, but this rarely required stopping use of the patch. No other important side effects emerged in the trials.

NICOTINE NASAL SPRAY AND NICOTINE INHALER

The nasal spray and the inhaler, not yet marketed, have each been tested in one published trial. The point prevalence estimates of efficacy were 15% (5% to 25%) for nicotine spray (in an antismoking clinic)[38] and 12% (5% to 20%) for the inhaler (in community volunteers).[39] Efficacy was thus little greater than the effect of 2 mg gum in these settings (table II). Irritant effects of the nasal spray affected almost all users, and habituation was a problem; at 12 months 13 (43%) of the abstainers were still using the spray.[38] Future trials may show advantages in combining newer delivery systems with a patch.

Discussion

Nicotine replacement therapy helps nicotine dependent smokers to stop smoking. The randomised trials of each form of treatment have shown a statistically significant effect.

DETERMINANTS OF EFFICACY

The efficacy of all forms of nicotine replacement therapy must rely to some extent on smokers being dependent on nicotine, and this was indeed the case. Ten trials of nicotine gum that measured nicotine dependence all showed a greater efficacy in highly dependent smokers ($P < 0.001$).[2,6,12,15,21,26-30] The association between efficacy of the gum and nicotine dependence (measured by the Fagerström score) was continuous,[12,30] but efficacy was low in smokers with Fagerström scores of 6 or less. The nicotine transdermal patch had little effect at the highest level of dependence. A likely explanation for this observation is that the slow absorption from the patch may be insufficient to relieve withdrawal symptoms in very dependent smokers; it cannot deliver a "bolus" of nicotine to satisfy craving.

Dosage also determined efficacy: direct evidence from randomised trials shows that the 21 mg transdermal patch is better than the 14 mg patch and, in smokers highly dependent on nicotine, 4 mg gum is

better than 2 mg gum. Several factors are likely to have contributed to the greater efficacy in self referred than in invited subjects. The self referred smokers are likely to have been more strongly motivated to give up smoking than invited smokers; a higher proportion of them were nicotine dependent; and their therapists provided greater encouragement. In the gum trials they were advised on correct chewing technique and were encouraged to use the gum regularly (regular use is more effective than discretionary use).

RECOMMENDED GUIDELINES FOR USE OF NICOTINE REPALCEMENT THERAPY

Nicotine dependence

The use of nicotine replacement therapy should be restricted to smokers who show evidence of nicotine dependence. Among such smokers the transdermal patch is probably the product of choice for all but the most heavily dependent. Its efficacy is at least as great as that of 2 mg gum (tables II and V) and it has the advantages of greater convenience, minimal need for instruction and encouragement, relative lack of side effects, and low risk of habituation. It is also appropriate for people with peptic ulcers (exacerbated by swallowing nicotine) and people with dentures, who may have difficulty using the gum. It is suitable for over the counter purchases, and since the daily cost of replacement therapy is about the same as a packet of 20 cigarettes in Britain there is no financial barrier to its use.

In the most highly nicotine dependent smokers the patch seems to have little effect.[36] The evidence indicates that the 4 mg gum is the most effective form of replacement therapy. It produces the highest blood levels of nicotine (figure), is effective in the most dependent smokers,[30] and enabled about a third of dependent subjects in the trials to stop smoking. Assessing a smoker's dependence should precede the decision to offer the 4 mg gum.The most discriminant indicators of dependence are the time to the first cigarette after waking and the number of cigarettes smoked per day,[49] but the entire Fagerström questionnaire (see appendix) is simple to complete. The 4 mg gum requires instruction on the correct chewing technique to reduce side effects and maximise efficacy, and users also need encourgement to use the gum frequently and to persist despite the unpleasant taste and side effects. Repeated consultations with a doctor or practice nurse are therefore desirable, and so the 4 mg gum should remain on prescription. Dependence on the gum may be a problem in some abstainers.

Safety in pregnancy

The manufacturers recommend that nicotine replacement is not used during pregnancy because of possible risk to the fetus. Benowitz has discussed this problem.[54] Maternal smoking is harmful to the fetus. It is not certain which are the toxic components, but nicotine is a serious candidate: it may contribute to fetal hypoxia and growth retardation through a reduction in placental blood flow. Nicotine replacement therapy could therefore be hazardous to the fetus. But it is likely to be less hazardous than moderate smoking since it produces a slower increase in plasma nicotine concentration, does not yield carbon monoxide or other noxious substances, and, if successful, does not expose the fetus to nicotine throughout pregnancy. It is better if a woman can stop smoking in pregnancy without using replacement therapy, but nicotine replacement may be justified if other methods fail.

Use in patients with coronary artery disease

The manufacturers of the gum and patches recommend caution in the use of nicotine replacement therapy in patients with cardiovascular diseases because of concern over possible circulatory effects of nicotine. This is unwarranted. Pipe smokers absorb nicotine through the buccal mucosa like nicotine gum users and they achieve higher plasma levels of nicotine and its metabolite than cigarette smokers, yet unlike cigarette smokers they have no material excess mortality from coronary artery disease.[55] Similar comments apply to users of snuff.[56] The direct effects of nicotine in increasing blood pressure and heart rate are short term and smaller than those caused by many common activities not regarded as hazardous. Also, smoking a cigarette does not commonly precipitate angina in patients with coronary artery disease. In any case the use of nicotine chewing gum (4 mg) has a smaller effect on blood pressure and heart rate than cigarette smoking.[54] If there is hazard at all it must be smaller than that of continuing to smoke. Nicotine dependent patients who are motivated but have not succeeded in stopping smoking without nicotine replacement can be advised to use this therapy.

Clinical implications

- Nicotine 2 mg chewing gum had an overall efficiency in helping people to stop smoking of 6% (11% in self referred subjects and 3% in invited subjects)
- Efficacy of nicotine gums depended on the extent of dependence on nicotine as assessed by a simple questionnaire
- The 4 mg gum was effective in about a third of "high dependence" smokers
- Nicotine patches were effective in 9% of smokers and were less strongly related to dependence
- Overall, nicotine replacement therapy could enable about 15% of smokers who seek help to stop smoking

CONCLUSIONS

Nicotine chewing gum and transdermal patch are both effective aids for nicotine dependent smokers who seek help in giving up. In the most highly nicotine dependent smokers (craving a cigarette on waking) nicotine 4 mg gum seems the most effective form of replacement therapy at present. With supervision and encouragement it should enable about a third of these smokers to give up smoking. Among less dependent smokers the transdermal nicotine patch is at least as effective as 2 mg gum and offers the advantages of greater convenience, minimal need for instruction, fewer side effects, and lower risk of habituation. Nicotine replacement therapy overall could enable about 15% of smokers who are motivated to seek help to give up smoking—a useful effect in overcoming a lethal habit.

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Appendix: the Fagerström test for nicotine dependence

Several of the trials used the Fagerström tolerance questionnaire, published in 1978.[48] It was modified in 1991, omitting questions of less discriminatory value and giving greater weight to more discriminatory questions.[49] This new version, reproduced below, has a maximum score of 10; scores are one less than those cited in the text from the original questionnaire. We suggest that nicotine 4 mg gum is used in the most highly dependent smokers (score of 8 or more) and the transdermal patch in less dependent smokers (scores of 4-7). The questionnaire is copyright but may be used by individual doctors for clinical purposes.

Questions	Answers	Points
1 How soon after you wake up do smoke your first cigarette?	Within 5 minutes	3
	6-30 Minutes	2
	31-60 Minutes	1
	After 60 minutes	0
2 Do you find it difficult to refrain from smoking in places where it is forbidden (eg, in church, in the cinema, at the library, etc)?	Yes	1
	No	0
3 Which cigarette would you hate most to give up?	The first one in the morning	1
	Any other	0
4 How many cigarettes a day do you smoke?	31 or more	3
	21-30	2
	11-20	1
	10 or less	0
5 Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6 Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0