Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation*

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Summary

Nicotine-replacement therapy (NRT) by gum, transdermal patch, intranasal spray, or inhalation is expensive but how effective is it? We have done a meta-analysis of controlled trials to see how effects on abstinence rates are influenced by the clinical setting, the level of nicotine dependency, the dosage of NRT, and the intensity of additional advice and support offered. Published or unpublished randomised controlled trials of NRT that have assessed abstinence at least 6 months after the start of NRT were identified and 53 trials (42 gum, 9 patch, 1 intranasal spray, 1 inhaler), with data from 17 703 subjects, were included in the analyses.

Use of NRT increased the odds ratio (OR) of abstinence to 1·71 (95% confidence interval 1·56–1·87) compared with those allocated to the control interventions. The ORs for the different forms of NRT were 1·61 for gum, 2·07 for transdermal patch, 2 92 for nasal spray, and 3·05 for inhaled nicotine. These odds were non-significantly higher in subjects with higher levels of nicotine dependence but they were largely independent of the intensity of additional support provided or the setting in which NRT was offered.

We conclude that the currently available forms of NRT are effective therapies to aid smoking cessation.

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Introduction

Nicotine replacement is a frequent component of strategies to help people stop smoking.[1] The first type to become widely available was nicotine chewing gum but oral and gastric side-effects[2] impaired absorption when taken with coffee or acid beverages,[3] and a risk that some smokers might transfer their dependency to the gum[3] limited its usefulness. Other forms of nicotine replacement, devised to get round some of the problems with nicotine gum, are transdermal patches, intranasal sprays, and inhalers. Nicotine sprays and inhalers have not yet been licensed for general clinical use.

Systematic reviews of the efficacy of nicotine gum have been published.[1,4,5] In 1987, a meta-analysis of 14 trials concluded that the gum was most effective when used in specialised smoking cessation clinics and that it was of questionable value when used in general practice.[5] A 1990 review confirmed those findings.[1] However, since then there have been over 20 new randomised trials of nicotine gum. Two reviews of nicotine patches,[6,7] published in 1992, suggested that this form is also highly effective, but neither review used comprehensive methods to identify all the published and unpublished trials, nor did they use quantitative techniques to synthesise the data and test for homogeneity or significance.

Since nicotine replacement therapy is widely available and costly, it is important to establish the efficacy of its different forms when offered to smokers with varying levels of dependency and motivation to quit and to do so in a range of clinical settings, with or without additional support.[8] We have done a systematic review by meta-analysis of all randomised trials of nicotine gum, patches, sprays, and inhalers, in which participants have been followed up for at least 6 months.

Methods

Study selection

We did a computerised search with the DataStar program on seven databases to identify trials published before March, 1993. We also examined published reviews, reference lists from clinical trials, conference abstracts, smoking-and-health bulletins, and a bibliography on smoking and health. To identify unpublished studies we wrote to the manufacturers of nicotine replacement products.

To be included in the meta-analysis a trial had to have at least two treatment groups with allocation by formal randomisation or by a quasi-random method such as alternation. Studies with historical controls were excluded. The review was confined to a comparison of effects on smoking cessation rather than withdrawal symptoms. Trials in which follow-up was less than 6 months were also excluded. Side-effects were not reviewed quantitatively because of the wide variation in reporting the nature, timing, and duration of symptoms.

Definitions

Cessation rates were identified from the published reports and we used the strictest criterion to define abstinence, when there was a choice. Where biochemical confirmation of cessation was provided only those participants who met that criterion were regarded as being abstinent. Sustained cessation rates were used in preference to a point prevalence. Patients lost to follow-up were regarded as being continuing smokers. The methodological quality of the studies was also assessed.[9]

The intensity of additional support was defined as low if it could be regarded as routine care. If the time spent with the smoker (including assessment for the trial) exceeded 30 min at the first consultation or if the number of further assessment and reinforcement visits exceeded two, the intensity was classified as high.

Where the methodology was unclear or results were not expressed in a form which allowed extraction of key data we wrote to the investigators for the required information.

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NRT preparation	Proportion quitting		OR (95% CI)	χ^2 test for heterogeneity
	NRT	Control		
Gum (n=39)	1149/6328 (18 2%)	893/8380 (10 6%)	1 61 (1 46–1 78)	$\chi^2_{38}=49\ 0$, p=0 11
Patches (n=9)	255/1245 (20 5%)	105/968 (10 8%)	2 07 (1 64–2 62)	$\chi^2_8=7\ 1$, p=0 53
Nasal spray (n=1)	30/116 (25 9%)	11/111 (9 9%)	2 92 (1 49–5 74)	Not applicable
Inhaler (n=1)	22/145 (15 2%)	7/141 (5 0%)	3 05 (1 42–6 57)	Not applicable
All NRT trials	1456/7834 (18 6%)	1016/9600 (10 6%)	1 71 (1 56–1 87)	$\chi^2_{44}=64\ 3$, p=0 07

Test for heterogeneity between different types of NRT ($\chi^2_3=8\ 49$, p=0 04).
Based on longest follow-up available for each trial (minimum 6 months).

Table 1: **Comparison of proportion of smokers who successfully quit with NRT versus control**

Statistics

The statistical methods used to pool the data involved calculating the typical odds ratio (OR) and its 95% confidence interval (CI) on the basis of a fixed-effects model.[10] Heterogeneity was tested for by a Mantel-Haenszel approach.[11] Results are expressed as the OR (NRT to control) for achieving abstinence from smoking at a given time point together. The number of smokers that would have to be treated to produce one successful quitter at 12 months was derived from the inverse of the pooled typical event rate difference.[12] In subgroup analyses we used 12-month abstinence rates wherever possible, except for studies providing only 6 months of follow-up data.

Results

53 trials were included (42 gum, 9 patch, 1 spray, 1 inhaled).† Except for 12 gum trials and 3 patch trials, participants were followed up for at least 12 months. Only 1 trial restricted participation to male smokers.

31 gum trials used the 2 mg dose and 2 used 4 mg; 5 used a variable or mixed dosage; and in 4 trials the dose was not stated. The therapy lasted 3 weeks to 12 months. Many trials included dose tapering, but most encouraged participants to stop using the gum after 6–12 months. In the patch trials, the minimum duration of therapy ranged from 6 weeks to 3 months, with a tapering period, if required, in 3 studies.

The extent to which bias was controlled varied considerably. 39 trials made no attempt to describe randomisation; only 12 had blinded validation of smoking status of all those who reported abstinence. 21 trials reported the smoking status at the final follow-up visit of all participants randomised, including those who had withdrawn before the final assessment.

Despite great variation in trial characteristics there was no statistical evidence of significant heterogeneity. Only 3 trials yielded a negative treatment effect for nicotine replacement (OR<1) at the end of follow-up, but in a further 31 trials the 95% CI included unity.

The four forms of nicotine replacement were all significantly more effective than placebo (or no therapy) in helping smokers to abstain. The benefit was evident throughout the 12 months of follow-up despite significant relapse rates. The odds of being abstinent at the four follow-up points during the 12 months remained fairly constant for each type of replacement.

When abstinence rates were pooled (table 1), according to the longest duration of follow-up available, 19% of those allocated to replacement and 11% of controls had successfully stopped smoking. This represents a 71% increase in the odds of abstinence with the use of nicotine replacement (95% CI 56–87%). On indirect comparison the OR for abstinence with transdermal patches was greater than with nicotine gum, though this was not significant ($\chi^2_1=3{\cdot}69$, p=0·05). Similarly the ORs for abstinence with the newer forms of NRT (nasal spray and inhaler) were greater than with either nicotine gum or transdermal patch ($\chi^2_3=8{\cdot}49$, p=0·04). For trials of nicotine gum and transdermal patch, the odds of not smoking were not affected by whether the control group was placebo or no therapy (not shown).

The pooled odds of abstinence in the two trials which directly compared 4 mg with 2 mg gums was 76% greater with the higher dose (OR 1·76 [95% CI 0·99–3·13]). Only 1 trial compared a "fixed" dose regimen of nicotine gum with an "ad lib" regimen; the fixed dosage regimen increased the odds of abstinence but this was not significant (OR 1·36 [0·92–2·00]).

1 trial directly compared the effect of wearing nicotine patches only whilst awake (about 16 hours) versus

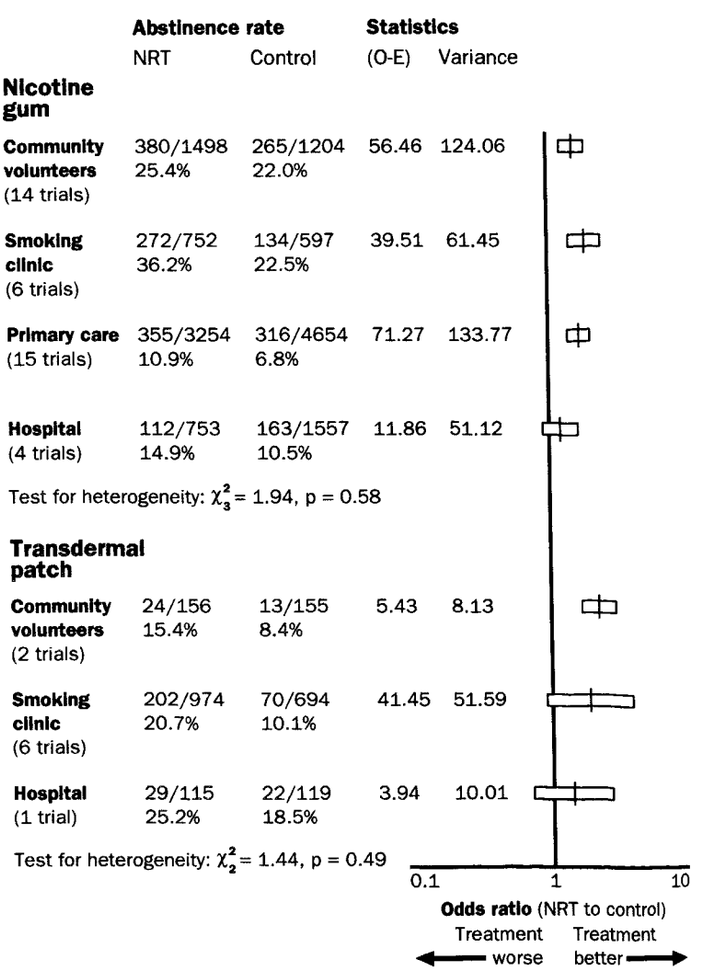

Figure: **Efficacy of nicotine gum and transdermal patches in different clinical settings**

Only pooled results for all trials within each subgroup shown. Graphical representation shows OR (vertical line) and 95% CI (box). Data are based on longest follow-up available for each study (minimum 6 months).

†A full list of trials is available from CS and appears in the *Online Journal of Current Clinical Trials* version of this paper.

Setting	Intensity of support	Gum	Patch	Nasal spray	Inhaler
Any	Unselective	29 (22–41)	11 (8–18)		
Any	High	26 (17–58)	9 (6–20)	6 (4–16)	10 (6–30)
Any	Low	29 (21–45)	12 (8–30)		
Community volunteers	Unselective	15 (10–27)	10 (7–18)		
Smoking cessation clinics	Unselective	10 (7–19)		7 (4–16)	10 (6–30)
Primary care	Unselective	35 (25–63)	14 (7–222)		
Hospital patients	Unselective	58 (22–NE)	15 (6–NE)		

= no trials available.
NE = treatment not effective (ie, typical event difference favours control).
Data based only on trials which provided 12 month follow-up result.

Table 2: **Estimate of number of smokers needed to treat with NRT to produce one successful quitter at 12 months**

continuous wearing (24 hours). The study found no significant difference in the self-reported odds of abstinence at 6 months follow-up but had low power (OR for 24 h *vs* 16 h 0·62 [0·26–1·47]).

The efficacy of nicotine gum relative to control was similar whether offered to smokers attending smoking cessation clinics, to those recruited from the community as volunteers, or to patients recruited opportunistically through primary care (figure). However, since the absolute abstinence rate was higher in community volunteers and smoking cessation clinics, the percentage of smokers helped to quit by using NRT was higher in these settings than in primary care or hospital patients.

The proportional increase in the odds of smokers helped to quit by using transdermal patches is similar amongst those recruited either as community volunteers or opportunistically through primary care, although the 95% CIs for the ORs in primary care are wide, due to the small number of trials with 6–12 month follow-up data. Smokers recruited as hospital inpatients, or through outpatient clinics, have a non-significantly lower odds of quitting with either gum or transdermal patches than smokers seen in other clinical settings, and the confidence intervals even include unity. The nicotine gum results in this setting are also strongly influenced by one large trial which had a negative effect. The results for transdermal patches are based on small numbers of patients, since there is currently only one completed trial.

Four trials of 2 mg nicotine gum versus control stratified their results according to the smoker's level of nicotine dependence, assessed using the Fagerstrom score.[13] The OR for abstinence was not significantly greater in high nicotine dependent smokers with Fagerstrom scores $\geqslant 7$ (OR 2·48 [1·43–4·31] compared with 1·18 [0·70–2·01] in the low-dependency group with Fagerstrom scores <7) ($\chi^2_1 = 3{\cdot}61$, $p = 0{\cdot}06$). Two trials compared 4 mg gum versus 2 mg gum in high nicotine-dependent smokers. The OR for abstinence was 2·7 (1·48–4·99) in favour of the 4 mg gum. Only one small trial compared 4 mg and 2 mg in smokers with low nicotine dependence; the results favouring the 2 mg dose (OR 0·27 [0·005–1·43]). There were insufficient data from the patch trials to stratify results according to the level of nicotine dependency.

To summarise the data from a clinical perspective we calculated the number of smokers who would require treatment with the various forms of NRT in order to produce 1 extra non-smoker at 12 months beyond the number who would achieve that with the control intervention (table 2).

The absolute probability of not smoking at 6–12 months was, not surprisingly, greater in trials which provided high-intensity additional support (19·7% [95% CI] 18·7–20·6%) rather than low intensity (10·5% [9·9–11·1%]). However, the OR for abstinence when nicotine gum was used in conjunction with low-intensity additional support (1·80 [1·54–2·11]) was not significantly different from the OR for abstinence when nicotine gum was used in conjunction with high-intensity support (1·48 [1·28–1·70]) ($\chi^2_1 = 3{\cdot}39$, $p = 0{\cdot}07$). Use of transdermal patches resulted in ORs of 2·14 (1·46–3·13) and 2·04 (1·51–2·74) with low and high intensity additional support, respectively; these ORs were not significantly different ($\chi^2_1 = 0{\cdot}04$, $p = 0{\cdot}49$). Only 2 small trials, both in primary care, directly compared the effect of providing high or low intensity follow-up to subjects receiving nicotine gum. The pooled results favour intensive follow-up but the result was not statistically significant (OR 1·30 [0·75–2·28]).

Discussion

This overview provides reliable evidence, from nearly 18 000 subjects, that offering NRT to smokers, either as the mainstay of a smoking cessation strategy or as an adjunct to other interventions, is more effective in helping them to stop smoking than when NRT is not offered or if placebo is used. This applies to all forms of NRT and is independent of any variations in methodology or design characteristics of trials included in the overview.

All forms of NRT were associated with a high relapse rate. Minimising this relapse is important if long-term smoking cessation rates are to be substantially improved. Although considerable caution is required in drawing conclusions from indirect comparisons of efficacy both the absolute abstinence rate and the odds of abstinence were non-significantly greater with transdermal patches than nicotine gum. In clinical terms, our best estimate is that the number of smokers who would need to be "treated" could be reduced by up to 60% by using transdermal patches rather than nicotine gum. Two newer forms of NRT also show considerable promise although further trials are required. In addition, trials are required which directly compare the different types of NRT.

The two factors which have been suggested as the major determinants of the effectiveness of NRT are the setting in which it is offered and the smoker's level of dependency on nicotine.[15] The nature and flexibility of the dosage regimen seem far less important.

In this review the OR for abstinence with nicotine gum and transdermal patches was slightly greater if offered to smokers recruited from the community or those attending specialised clinics than if offered to smokers in primary care. However, these differences were not significant. Even if they had been, the number of specialised clinics will always be small so that access will be restricted to a small proportion of smokers wanting help to quit. The poor result seen with use of nicotine gum in hospital-based patients was disappointing given that these patients frequently had coexisting smoking-related diseases which might have been an added incentive to quit.

The benefit seen in previous studies of nicotine gum in smokers with high levels of dependency in nicotine is supported by the findings in this review although the difference in the ORs in the groups just failed to reach statistical significance. Further data from patch trials is required where abstinence rates are stratified according to the level of nicotine dependency.

Addition of a high, rather than low, intensity support programme only reduced the number of smokers who needed to be treated with nicotine gum to produce 1 extra non-smoker at 12 moths from 29 to 26. For transdermal patches, the corresponding figures are 12 and 9, respectively. Smokers must not interpret these results as indicating that NRT offers an easy option "medical cure" for the far more complex problem of addictive behaviour. All the trials in this review included some form of support additional to NRT and it would be incorrect to conclude that such additional support is not necessary.

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"Occult" hepatitis B virus as source of infection in liver transplant recipients

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Summary

Hepatitis B virus (HBV) infection almost always recurs after liver transplantation in patients who were surface antigen (HBsAg) positive before surgery but apparent de novo acquisition of infection in a transplant setting has not previously been reported. We have used sensitive techniques to elucidate the origin of such infections in patients in a Californian transplantation programme.

We tested post-transplant serum from 207 patients who had been HBsAg negative and found 20 to be HBsAg positive. The origin of infection was identified in 7 patients, being occult pre-transplant infection in 5 and occult infection in the donor in 2. No pre-transplant patient nor donor with demonstrable HBV DNA had serological markers of hepatitis B. Post-transplant HBV DNA was present in serum from 19 patients. Analysis of the variable pre-S region of HBV demonstrated 100% sequence homology between recipient liver and post-transplant serum (2 patients) and between donor serum and recipient post-transplant serum (2). There was only 84% homology between the 2 different patients infected with subtype adw. 19 patients are alive, 9 without histological evidence of hepatitis (mean follow-up 33 months), and survival was significantly greater than that of a group with recurrent HBV infection.

Apparent acquisition of HBV infection with liver transplantation is not rare, and may be due to occult pre-transplant infection or occult infection in the donor. The post-transplant outcome of this infection tends to be benign but our findings do underscore the clinical relevance of HBV infection in the absence of serological markers.

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Introduction

The frequent recurrence of hepatitis B virus (HBV) infection after liver transplantation and the unusual severity of such recurrences are well recognised. The clinical, histological, and virological features of these recurrences have been extensively described[1,2] but there have been no reports of apparent acquisition of HBV infection. We describe here 20 patients who had liver transplantation for disease thought unrelated to HBV but who became hepatitis B surface antigen (HBsAg) positive after the operation. Using the polymerase chain reaction (PCR) we sought the source of that infection and by nucleotide sequence analysis we looked for homology between the nucleotide sequences of the original virus and of that causing post-transplant infection.

Patients and methods

Patients

Between February, 1988, and October, 1991, 275 patients underwent liver transplantation at the University of California, San Francisco. 41 were excluded from the primary study group (23