

## ORIGINAL ARTICLE

# Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support

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**Background:** Smoking is a major public health issue, estimated as causing 120 000 deaths in the UK per year. Smoking cessation is an important aspect of the treatment of many diseases. Nicotine replacement therapy (NRT) has been shown to increase cessation rates among healthy volunteers and in general practice, but it is not clear whether it has an effect in hospital patients.

**Methods:** Patients referred by their hospital doctor to the smoking cessation counsellor and who agreed to participate in the study were randomised to receive either NRT given as a nicotine patch daily and a nicotine inhalator on an as needed basis plus advice and support (AS+NRT), or to receive just advice and support (AS). Claims of smoking cessation were validated at 1 week, 3 months, 6 months, and 1 year by carbon monoxide (CO) breath testing.

**Results:** A total of 245 patients were randomised, 136 AS+NRT and 109 AS. There were no significant demographic differences between the two groups at baseline. At 1 year 35 (14%) had sustained cessation confirmed by a CO breath test, 20/136 (15%) AS+NRT and 15/109 (14%) AS,  $p=0.857$ . One hundred and ten patients gave up smoking for at least 1 week, 54% AS+NRT and 33% AS ( $p<0.001$ ). By 6 months there was no significant difference between the two groups (22/136 (16%) AS+NRT and 15/109 (14%) AS).

**Conclusion:** In hospital patients NRT, given as regular daily patches plus an inhalator to be used as needed, did not add to the smoking cessation rate achieved at 1 year by regular advice and support, despite significantly increasing the cessation rate at 1 week.

Doll and Hill first published their results on smoking and carcinoma of the lung in 1950. At that time 80% of men and 40% of women were smokers. Although among those aged over 50 years there are twice as many individuals who are ex-smokers than smokers,<sup>1</sup> mortality and morbidity due to smoking related diseases is still a major health issue with an estimated 120 000 deaths per year in the UK directly caused by smoking.<sup>2</sup> Smoking thus remains the largest single preventable cause of death<sup>2,3</sup> and, with a current smoking prevalence of 28% of the UK population,<sup>2</sup> there is much work to be done. It is estimated that, if the UK government achieved its target of cutting the proportion of smokers to 26% by 2005 and 24% by 2010, the NHS would save £524m in prevented strokes and heart attacks in addition to savings made in other smoking related diseases such as lung cancer,<sup>4</sup> so the gains from effective smoking prevention and cessation management are considerable. Smoking prevention is probably the most important method of reducing numbers of smokers in the population but this is an area for government and legislation. Helping patients to stop smoking, especially those with smoking related diseases, is the responsibility of doctors and other health professionals.

Many trials have assessed the effects of nicotine replacement therapy (NRT) in smoking cessation but most of these have studied as yet healthy smokers recruited through advertising in the media.<sup>5–9</sup> The Cochrane database review of NRT concludes that it increases quit rates by 1.5–2-fold, regardless of setting,<sup>10</sup> yet all but two of the trials included only healthy volunteers. There were very few negative studies and, although the authors did send letters to manufacturers of NRT preparations for additional data, none were obtained. Healthy volunteers entering a trial are likely to be highly motivated to quit smoking whereas patients who have persisted with the habit despite their illnesses represent a hard core group of

smokers.<sup>11</sup> We feel that it is not appropriate to draw conclusions about smoking cessation in patients from studies on healthy individuals.

A previous study using nicotine gum versus placebo revealed no significant increase in cessation rate among hospital patients.<sup>12</sup> A further study using transdermal nicotine patches showed increased smoking cessation compared with placebo (21% v 14% at 1 year), but this difference was not statistically significant.<sup>13</sup> Different nicotine delivery systems have reported success rates ranging from 17% to 35%.<sup>5–8, 14, 15</sup> It may be surprising that the success rate is not higher, but perhaps none of these delivery systems can mimic the unique way in which the cigarette delivers nicotine.<sup>16</sup> A previous study has shown success using both a patch and a nasal spray in healthy volunteers.<sup>5</sup> The aim of our study was to investigate if this success could be replicated in hospital patients using another combination of two forms of NRT—a patch to supply a steady blood level and a nicotine inhaler to be used as needed to boost the blood level, much as a cigarette might act.

We were unable to obtain support for this study from a pharmaceutical company and used funding from one author's endowment fund. Financial constraints were an important limiting factor in the design of this study.

## METHODS

### Eligibility criteria

Eligible patients were hospital inpatients or outpatients with smoking related disease referred to the counsellor by their hospital doctor and aged 18 years or over. Patients excluded were those with alcoholism, drug dependency, active psychiatric illness, preterminal or terminal patients, pregnant women, and those who had suffered a myocardial infarction during the previous month.

### Study design

The study was designed to be able to detect a clinically significant enhancement of sustained abstinence with NRT at 1 year. A sample size of 242 was required to detect a difference of 15% with abstinence rates of 30% for NRT and 15% for counselling only, with 80% power, and a 5% significance level using a two tailed test. We considered these proportions appropriate since the published data suggest doubling of cessation rates with NRT,<sup>10</sup> and cessation rates with just counselling in our department had previously been about 20%.<sup>12, 13</sup>

Patients were advised by their physician to stop smoking. Those who were willing to see the smoking cessation counsellor were referred. The counsellor saw the patients, reiterated the advice to stop smoking, gave them literature on smoking, and invited them to enter the study. Those who consented were randomised, according to month of entry, to receive either advice and support only (AS) or NRT and advice and support (AS+NRT). Recruitment began on 1 October 1998 and all patients recruited during that month and in any even month over the next 13 months were given NRT. Those recruited the following month and in any odd month over the next 12 months were given only advice and support. Patients were enrolled in the trial until at least 242 had been recruited. Recruitment stopped on 31 October 1999 when 245 patients had been entered. Because of the simple form of randomisation there was one extra month of patients randomised to receive NRT, leading to unequal numbers in the two groups.

The counselling programme was undertaken by the same person (SE) for all patients. The programme started with four weekly sessions during which time the patient was encouraged to set a "quit date" within 7 days of the first visit. The initial session of 45–60 minutes involved a detailed smoking history, as outlined previously,<sup>17</sup> and support literature was given to the patient. This session was followed by three further weekly sessions, each lasting 15–30 minutes. If the patient was unable to stop smoking during this 4 week period s/he was withdrawn as a failure. Smoking cessation was validated by breath carbon monoxide (CO) levels of less than 10 ppm at 1 week after the quit date. At 1 month the patient was asked to attend and smoking cessation was validated again. At 2 months the patient was contacted by telephone or by letter to encourage and support. At 3 months the patient was seen by the counsellor again and smoking cessation validated by CO measurement. At 5 months the patient was again contacted by telephone or letter and then cessation was validated again at 6 months. At 9 months the patient was contacted and seen with CO validation at 12 months.

Patients were encouraged to contact the counsellor for support and advice between appointments. In addition, those randomised to NRT received for 3 weeks a combination of regular nicotine patches and on demand nicotine inhalator (up to 14 refills a week), all provided at their first appointment. Both these products were bought by the authors from a reputable chemist and given free of charge to the patients.

The dose of the nicotine patch was determined by the number of cigarettes smoked. Those who smoked more than 20 cigarettes per day were given a 30 mg patch for the first week, 20 mg for week 2, and 10 mg for week 3. Those who smoked less than 20 cigarettes per day were given 20 mg patches for the first 2 weeks and a 10 mg patch for week 3. In addition to the patches, all those in the NRT group were given a nicotine inhalator starter pack containing six cartridges and a refill pack containing a further 42 cartridges. The inhalator has a replaceable nicotine cartridge and a mouth piece. Each cartridge provides 10 mg nicotine which the manufacturer advises is appropriate for 20 minutes of heavy use. One cartridge can be used several times. The inhalator therefore provided a total of 480 mg nicotine replacement for each patient for the 3 weeks or a further 20 mg nicotine per day if required.

**Table 1** Comparison of treatment groups by demographic factors at entry to study

Factors	AS (n=109)	AS+NRT (n=136)	p value ( $\chi^2$ test)
Age (years)			
<40	10	21	0.1309
40–49	18	33	
50–59	34	35	
≥60	47	46	
Sex			
Male	55	57	0.1821
Female	54	79	
Disease			
IHD + risks	22	29	0.9491
COPD	40	54	
Other lung disease	29	31	
Vascular disease	6	6	
Other disease	12	16	
No of cigarettes smoked			
≤15	29	37	0.4636
16–25	49	51	
>25	31	47	
Partner smokes			
Yes	38	68	0.0540 (including no partner) p = 0.1200 (excluding no partner)
No	32	35	
No partner	38	33	
Not stated	1	0	

NRT = nicotine replacement therapy; AS = advice and support; IHD + risks = ischaemic heart disease and risk factors for this (hyperlipidaemia, diabetes, family history, etc); COPD = chronic obstructive pulmonary disease.

Smoking cessation was validated by CO breath test at 1 week, 3 months, 6 months, and 1 year. Success was defined as verified non-smoking at each of these time points with claimed non-smoking between these times. Non-attenders were classified as failures.

### Statistical methods

Data analysis was performed using the  $\chi^2$  test employing SPSS software. Statistical significance was taken as  $p < 0.05$ .

### RESULTS

Between October 1998 and December 1999 a total of 423 patients were referred to the smoking cessation counsellor. Eighty four (20%) did not attend. Of the 339 who did attend, 94 (28%) were unwilling to enter the trial. The remaining 245 patients (112 men) were randomised, 109 to the AS group and 136 to the AS+NRT group. Of those in the NRT group, 44% received the higher dose of nicotine patches (30 mg, 20 mg, 10 mg) and 66% the lower dose of nicotine patches (20 mg, 20 mg, 10 mg). All received in addition 48 cartridges of 10 mg nicotine inhalators. There was no significant difference between the demographic characteristics of the two groups at entry to the trial (table 1).

At 1 year 35 (14%) of the total group were verified as abstinent at 1 week, 3 months, 6 months and 1 year and said that they had not smoked between these time points, 15 (14%) in the AS group and 20 (15%) in the AS+NRT group (table 2). At 1 week 110 (45%) patients were confirmed by a CO breath test as non-smokers, 36 AS and 74 AS+NRT ( $p < 0.001$ ). However, by 6 months the difference had disappeared. There was no significant difference in patient characteristics for smoking cessation (table 3), nor was there a significant difference between disease type and smoking cessation at 1 week (heart disease 21/51 (41%), lung disease 69/154 (45%), other disease 20/40 (50%),  $p = 0.702$ ).

### Compliance

All 136 patients randomised to receive NRT were issued with NRT but 28% did not use it; 30% used the full supply (table 4).

**Table 2** Rates of sustained abstinence from smoking for 1 week, 1 month, 3 months, 6 months, and 1 year and level of significance of differences between the two groups

Sustained abstinence	AS	AS+NRT	p value ( $\chi^2$ test)	Odds ratio (95% CI)
For 1 week: 110/245 (45%)	36/109 (33%)	74/136 (54%)	<0.001	2.42 (1.44 to 4.08)
For 1 month: 78/245 (32%)	28/109 (26%)	50/136 (37%)	0.073	1.68 (0.974 to 2.92)
For 3 months: 57/245 (23%)	22/109 (20%)	35/136 (26%)	0.362	1.37 (0.75 to 2.51)
For 6 months: 37/245 (15%)	15/109 (14%)	22/136 (16%)	0.720	1.21 (0.59 to 2.46)
For 1 year: 35/245 (14%)	15/109 (14%)	20/136 (15%)	0.857	1.08 (0.52 to 2.23)

AS=advice and support; NRT = nicotine replacement therapy.

**Table 3** Patient characteristics and smoking cessation at 1 year

Factors	Estimate (SE)	Odds ratio	p value	No of cases
Constant	-0.66 (0.79)	0.515	0.515	
Sex				
Male	0.00	1.00		112
Female	-0.19 (0.45)	0.827	0.675	133
Age (years)				
<50	0.00	1.00		82
≥50	-0.70 (0.55)	0.497	0.204	162
Diagnosis				
Heart disease	0.00	1.00		51
Lung disease	-0.36 (0.77)	0.695	0.637	154
Other disease	0.01 (0.66)	1.009	0.989	40
Treatment				
AS+NRT	0.00	1.00		136
AS	-0.70 (0.55)	0.972	0.951	109
Cigarettes smoked (per day)				
<20	0.00	1.00		145
≥20	-0.70 (0.46)	0.498	0.128	99
Partner smokes				
Yes	0.00	1.00		106
No	-0.64 (0.46)	0.530	0.168	67

AS = advice and support; NRT = nicotine replacement therapy.

**Table 4** Compliance in the nicotine replacement therapy (NRT) group and success at 1 year

	No (%) of patients	No (%) of successes
Never used NRT	38 (28%)	1 (2.6%)
Used full supply	41 (30%)	18 (43.9%)
Smoking before used full supply	46 (34%)	0
Terminated use because of allergic reaction	11 (8%)	1 (9.1%)

Thirty four percent started smoking again before they used the full supply and a further 8% terminated use of the patches because of allergic reactions. The successes in this group were in those who used the full supply with the exception of two individuals, one who never used NRT and one who stopped taking NRT because of an allergic reaction.

## DISCUSSION

Most previously published studies which have shown a significant effect of NRT on smoking cessation have been on healthy volunteers recruited by advertisements in the media. Two studies using NRT did not find a significant benefit in

hospital patients in terms of sustained validated cessation for at least 1 year.<sup>12, 13</sup> Other studies of hospital patients have reported only the point prevalence of cessation at 6 months<sup>18</sup> or have only followed up patients for 12 weeks.<sup>19</sup> However, neither of these studies showed a significant benefit of NRT. In this study we have again been unable to show a lasting benefit of NRT using the combination of regular patches and on demand inhalator.

We gave a large dose of NRT, up to 50 mg per day for the heavier smokers. The limited funds available for this study made us keen to use the shortest length of treatment that we felt might be effective. We opted for 3 weeks because other studies have found that most patients who quit do so in the first week.<sup>20, 21</sup> This, however, may not have been long enough since it is worth noting that, of the 41 patients who took the patches for the full 3 weeks without smoking, 18 were successful non-smokers at 1 year. Twenty three patients quit for 3 weeks with the help of patches but took up smoking again after 3 weeks. It is tempting to speculate that availability of NRT for a longer period might have permitted an effect to emerge, but this is not supported by the results of the two previous studies of NRT in our department<sup>12, 13</sup> nor by the result of the original study by the British Thoracic Society.<sup>22</sup> Because of the lack of pharmaceutical assistance we were unable to supply a placebo patch and inhalator which meant that our study was of an open design rather than single or double blind; however, if this was to affect the results at all, it would

have been more likely to bias the results towards NRT rather than the other way.

The usual cessation rate in our department has been 20%. In this cohort we were only able to obtain a 14% quit rate, perhaps because patients with recent myocardial infarction were not included and also because there were 21 more women than men among the 245 patients, and women tend to have lower cessation rates than men.<sup>23–24</sup> Furthermore, 94 of the 339 patients who attended the first appointment declined to participate in the study, rendering our cohort even more different from those normally going through the programme.

In our study cohort no single group had a better long term outcome in terms of smoking cessation at 1 year—that is, older age, sex, or partner's smoking habits did not have a significant effect on outcome. We analysed the 1 week success rates in terms of disease states and found no significant difference between diseases. In the AS + NRT group there were more women and more individuals with partners who smoked, features which are associated with lower cessation rates.<sup>23–25</sup> Although these differences between the two groups did not individually achieve statistical significance, it is possible that their combined effect might have biased the results against NRT.

Our results indicate that NRT given for 3 weeks as regular patches plus inhalator as required does not increase the smoking cessation rate at 1 year in a cohort of hospital patients in South Wales. However, NRT did increase the initial quit rate significantly. Our study has not looked at the long term effects of a single quit attempt that lasts a week, but there is some evidence that smokers who have abstained for a significant time in the past are more likely to quit in the future,<sup>26</sup> and that NRT may help the smoker to achieve that first attempt. It would therefore be presumptive to state that NRT has no place in hospital patients with smoking related diseases. More studies are needed to establish its place, if any, in this group.

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