Respiratory Medicine (1996) **90**, 47–51

Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study

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Background. Cessation rates in smokers attending special clinics or their General Practitioners can be increased by transdermal nicotine (TNS). This study assesses the efficacy of TNS as an adjunct to advice and support in helping patients attending hospital with smoking-related diseases to stop smoking.

Methods. In a double-blind, placebo-controlled, randomized manner, 234 inpatients and outpatients with smoking-related respiratory or cardiovascular disease, aged 18–75 years, who were willing to try to stop smoking, were advised by their hospital doctor to stop smoking. This was reinforced by repeated advice and encouragement from the Smoking Cessation Counsellor initially and at 2, 4, 8 and 12 weeks, supplemented by a 24 h patch in adjusted doses over that period. Those not smoking at 12 weeks were followed up at 26 and 52 weeks. Self-reported complete abstinence from 12 to 52 weeks was validated by expired air carbon monoxide measurement at 12, 26 and 52 weeks.

Results. Twenty-four (21%) of 115 TNS patients were verified as non-smokers at 12, 26 and 52 weeks and claimed continued abstinence, compared with 17 (14%) of 119 in the placebo (P) group ($P=0{\cdot}15$) – 5% confidence limits for odds ratio of abstinence on TNS compared to P: 0·83, 3·37. Cessation was related to increasing age ($P=0{\cdot}02$) and lower Fagerstrom score ($P=0{\cdot}05$). Minor skin reactions were more frequent in the TNS group (47% TNS; 34% P), as was nausea (12% TNS; 3% P). Severe skin reactions were rare (5% TNS; 4% P).

Conclusion. The suggestion that TNS produces an increase of 50% in relative terms (7% absolute increase) in smoking cessation over placebo in this population of hospital patients is sufficiently strong to warrant a further study large enough to answer whether or not this result was due to chance.

Introduction

Transdermal nicotine (TNS) is effective when used in specialized smoking cessation settings (1,2) and in general practice when used as an adjunct to support and counselling (3,4). For hospital patients with smoking-related diseases, moderate levels of advice and support, with or without nicotine chewing gum, resulted in 20% sustained cessation at 1 yr (5) which is much better than the success rates when minimal amounts of advice and support were used in similar populations (6,7). In outpatients, Foulds *et al.* (8) observed 13·7% abstinence at 12 weeks with TNS compared with 10·5% for placebo patches ($P=0{\cdot}15$). The present study includes inpatients as well as outpatients and reports cessation at 1 yr.

Received 8 November 1994 and accepted in revised form 27 May 1995.

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Patients and Methods

PATIENTS ELIGIBLE

Hospital inpatients and outpatients with smoking-related respiratory or cardiovascular disease, aged 18–75 years, who were willing to try to stop smoking. They must have smoked >1 cigarette daily within 1 week prior to admission to hospital or attendance at outpatients.

PATIENTS NOT ELIGIBLE

Cigar or pipe smokers, those with hypersensitivity to any adhesive cutaneous application, any skin disease, myocardial infarction within the previous month, severe cardiac arrhythmias, pregnancy or lactation, patients with mental disturbances and patients with terminal or pre-terminal cancer.

Design and Method

Patients were advised by their physicians to stop smoking. The Smoking Cessation Counsellor (ST-B)

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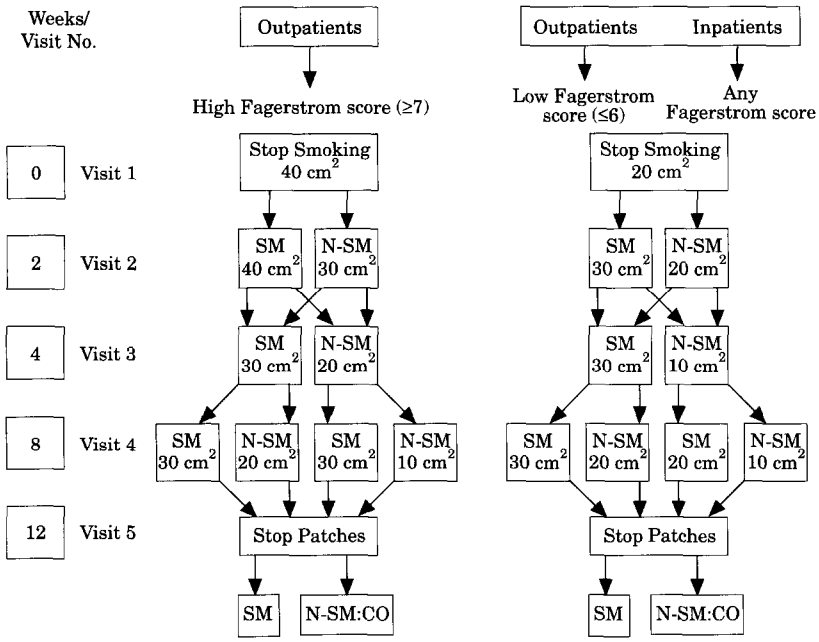

Figure 1 Nicotine *vs.* placebo patch: initial 12 weeks. SM, smoker; N-SM, non-smoker (no cigarette between two visits, except at 12 weeks when no cigarette for previous 48 h); CO, carbon monoxide measurement.

later asked those patients who fitted the inclusion criteria whether they would try to stop smoking. If they agreed, these patients were invited to enter the trial. Written, informed consent was obtained from each participant and the study passed by the local Ethics Committee. Patients were stratified according to their in/out-patient status and outpatients further stratified according to the level of nicotine dependence as measured by the Fagerstrom score (9). Outpatients with a high Fagerstrom Score (≥ 7) were randomized to 40 cm^2 nicotine (TNS) or placebo (P) patches and those who scored ≤ 6 were prescribed a 20 cm^2 TNS or P patch. Inpatients, already abstinent by virtue of being in a hospital ward, were randomized to 20 cm^2 TNS or P patches regardless of their Fagerstrom score. At the first encounter, ST-B discussed smoking cessation with each patient, and spent 30–60 min doing this, issuing the patches and giving instruction on their use.

DRUGS AND DOSAGE

The 30 cm^2 transdermal nicotine patch contained 52·5 mg nicotine, delivering 21 mg day^{-1}. The 20 cm^2 transdermal nicotine patch contained 35 mg nicotine, delivering 14 mg day^{-1}. The 10 cm^2 transdermal nicotine patch contained 17·5 mg nicotine, delivering 7 mg day^{-1}. Patients in the P group received a transdermal formulation with a very low content of nicotine (13% of the active form), a dose which is conventionally felt to be too low to affect outcome.

Treatment lasted 12 weeks during which period all patients were asked to return to the Outpatient Clinic to see ST-B at 2 weeks, 4 weeks, 8 weeks and 12 weeks, dosage being altered at each visit according to their smoking status (Fig. 1). At each return visit, support and encouragement were given to the patient and patient compliance estimated by counting used and unused patches. A direct question about smoking status was asked, and those who claimed not to have smoked at all between visits were classed non-smokers. Dosage was adjusted accordingly in these patients. Local and systemic tolerability of the patches were assessed by direct questioning. Each visit lasted between 15–30 min. At the 12-week visit, those who said they had not smoked for the previous 48 h and whose statement was verified by a reading of 7 ppm or less on the Bedfont Micro Smokerlyzer carbon monoxide meter were given an appointment for 3 months later (6 months from trial entry). Those claiming continuous abstinence at 6 months and whose statements were validated by measurements of expired air carbon monoxide were asked to return at 12 months and the assessment repeated. Patients who had been classed as smokers at 12 weeks were not followed-up.

Table 1 Results at 3 and 12 months

	Transdermal nicotine	Placebo	*P*-value
No. patients	115	119	
Abstinent at 12 weeks	37 (32%)	30 (25%)	0·21*
Sustained abstinence 3–12 months	24 (21%)	17 (14%)	0·15*
Nausea	14 (12%)	4 (3%)	0·02†
Erythema/oedema/itch	54 (47%)	40 (34%)	0·05†

*Calculated from linear logistic model incorporating treatment group, sex, and stratification category. †Chi-squared test.

STATISTICAL ANALYSIS

The planned sample size for the study was 100 patients per treatment group. This was based on 80% power to detect a statistically significant difference at the 5% level, if the absolute difference in cessation rate was 20%.

Comparison of proportions between the two treatment groups was by the Chi-squared test with Yates' correction for continuity. In order to investigate which variables were predictive of successful smoking cessation and to adjust for imbalances between treatment groups after randomization, a multiple linear logistic regression was employed.

Table 2 Success rates by stratum and treatment

Stratum		Success at 1 year *n*	Success at 1 year %
1	TNS	4/49	8·1
	P	8/51	15·6
2	TNS	12/36	33·3
	P	6/36	16·6
3	TNS	8/30	26·6
	P	3/32	9·3
Test of treatment interactions		χ^2=4·3 *P*-value=0·12	

Where Stratum 1, Outpatient/high dependency; Stratum 2, Outpatient/low dependency; Stratum 3, Inpatient. TNS, transdermal nicotine; *P*, placebo.

Results

Two hundred and thirty-four patients (54% female) entered the study from April to December 1990, 172 (74%) were outpatients (100 with high Fagerstrom score, 72 low) and 62 were inpatients (38 with high Fagerstrom score, 24 low). Mean age was 49 years (range 18–75, SD 13·3). Three out of four patients had respiratory disease. The mean duration of smoking was 31 yr (SD 13) in both treatment groups and the patients were equally divided among those smoking 1–15 cigarettes day^{-1}, 16–25 cigarettes day^{-1}, and more than 25 cigarettes day^{-1}, with a slight excess of heavy smokers in the TNS group. Eighty-five percent of the TNS patients had previously attempted to stop smoking, compared to 80% in the P group. There were more females in the TNS group (58%) than the P group (50%) and therefore sex was included in the linear logistic model used for analysis. There were no other important pre-treatment differences between the groups. The sample size was greater than planned because of a faster than expected recruitment rate.

A total of 113 patients (57 TNS, 56P) did not complete 12 weeks in the study, 21 (14 TNS, 7P) because of adverse events, and 92 (43 TNS, 49P) who failed to attend for follow-up by this stage. Thirty-seven (32%) patients in the TNS group and 30 patients (25%) in the P group were confirmed non-smokers at the end of 12 weeks (Table 1). By the end of 1 yr, 24 (21%) patients in the TNS group and 17 (14%) patients in the P group said they had not smoked throughout the period from week 12 to week 52 and had expired air carbon monoxide tests <7 ppm at 12, 26 and 52 weeks. This difference was not significant at the 5% level. There was no statistically significant interaction between stratum, treatment and outcome (Table 2).

If the analysis is restricted to those patients who used the patches as instructed, or withdrew due to adverse events or lack of efficacy, the population available falls to 166 patients; 87 TNS and 79P. The verified, sustained abstinence rates then become 22% TNS and 13% P (Logistic regression; P=0·13).

Successful cessation (sustained absence from 12–52 weeks) was significantly related to increasing age ($P=0{\cdot}02$) and to lower Fagerstrom score ($P=0{\cdot}05$) when a stepwise logistic regression was performed. Successful cessation was not related to in- or out-patient status, diagnosis, sex, number or length of time smoked cigarettes, or to previous attempts to stop smoking.

Although more patients in the TNS group complained of itch and/or erythema and/or oedema (Table 1), the frequency of skin reactions severe enough to cause treatment to be discontinued was similar in both groups (5% TNS cf. 4% P). Nausea was reported by 12% TNS *vs.* 3% P (Table 1). The majority of patients who experienced nausea had continued to smoke while using the patches (TNS 12/14; P 3/4).

Discussion

Patients who continue to smoke when suffering from smoking-related diseases severe enough to warrant referral or admission to hospital must be hard-core smokers. Previous studies have demonstrated how few of these patients (10–13%) gave up smoking in response to doctor's advice, even when advice was supplemented by simple support strategies (6, 7). At Llandough Hospital, the 12 months' success rate for advice and support supplemented by either nicotine gum or placebo gum was 20% (5). At Sahlgrens Hospital in Sweden, more intensive support combined with nicotine chewing gum improved the cessation rate to 29% and was superior to placebo (16% cessation) in a group of whom two-thirds were patients and the remainder were self-referred smokers (10). In the present study, nicotine patches used together with support have produced results in the same range, with a suggestion of superiority over placebo patches (21% cf. 14%, $P=0{\cdot}15$). Increasing age was again found to be a predictor of success, as was a low nicotine dependency score, but male sex and cardiovascular disease, predictors in previous studies (6,7), were not so in this study. However, a trend was present for male sex and cardiovascular disease, and the lack of significance may be due to inadequate power.

The results at 12 weeks were twice as good for TNS and placebo compared with those of Foulds *et al.* (8). The differences may be related to the natures of the populations studied and to the counselling. It would be interesting to know the success rates at 1 yr in Foulds *et al.*'s study, as it would in the study by DeBusk *et al.* (12) which reported 70% cessation at 2 months in patients admitted to hospital with myocardial infarction.

The relatively high rates of skin reactions in both groups indicate that there is much scope to improve the patch constituents in contact with the skin, although it is likely that TNS will still be more irritant than placebo (3,11). More of the patients in the present study experienced nausea than in the other two studies in general practice (3,11), perhaps because the present study used higher doses for some patients. In contrast to those studies, the patients in the present study rarely mentioned sleep disturbance.

The 50% increase in success rate of TNS relative to placebo (7% absolute increase) may or may not have been a chance finding. A further study large enough to answer this question should be conducted and should also, ideally, include a third group receiving support and advice without patches.

Acknowledgements

We thank Ciba-Geigy Ltd for funding this study and for providing Nicotinell TTS and placebo patches. The co-operation of members of staff at Llandough Hospital is gratefully acknowledged, as is Mrs S. Colman's and Mrs D. Wyatt's help with the manuscript.

References

1. Buchkremer G, Bents H, Minneker E, Opitzk K. Combination of behavioural smoking cessation therapy with transdermal nicotine substitution: long-term effects. In: Aoki M, Hisamichi S, Tominaga S, eds. *Smoking and Health.* Amsterdam: Excerpta Medica, 1987, 857–860. (International Congress Series No. 780).
2. Buchkremer G, Minneker E, Block M. Smoking cessation treatment combining transdermal nicotine substitution with behavioural therapy. *Pharmacopsych* 1991; **24:** 96–102.
3. Russell, MAH, Stapleton JA, Feyerabend C *et al.* Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *BMJ* 1993; **306:** 1308–1312.
4. ICRF General Practice Research Group. Randomised trial of nicotine patches in general practice – results at one year. *BMJ* 1994; **308:** 1476–1477.
5. Campbell IA, Tjeder-Burton SM, Prescott RJ. Smoking cessation in hospital patients given repeated advice plus nicotine or placebo chewing gum. *Respir Med* 1991; **86:** 155–157.
6. British Thoracic Society. Comparison of four methods of smoking withdrawal in patients with smoking-related diseases. *BMJ* 1983; **286:** 595–597.
7. British Thoracic Society. Smoking cessation in patients: two further studies by the British Thoracic Society. *Thorax* 1990; **45:** 835–840.
8. Foulds J, Stapleton J, Hayward M *et al.* Transdermal nicotine patches with low intensity support to aid

smoking cessation in out-patients department in a general hospital: a placebo-controlled trial. *Arch Fam Med* 1993; **2:** 417–423.
9. Fagerstrom K. Measuring degree of dependence to tobacco smoking with reference to individualisation of treatment. *Addict Behav* 1978; **3:** 235–241.
10. Hjalmarson IAM. Effect of nicotine chewing gum in smoking cessation. A randomised placebo controlled double-blind study. *JAMA* 1984; **252:** 2835–2838.
11. ICRF General Practice Research Group. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomised trial in general practice. *BMJ* 1993; **306:** 1304–1308.
12. DeBusk RF, Miller NH, Superko HR *et al.* A case management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med* 1994; **120:** 721–729.