Which smokers are helped to give up smoking using transdermal nicotine patches? Results from a randomized, double-blind, placebo-controlled trial

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SUMMARY

Background. *Nicotine replacement therapy is effective in helping people to give up smoking. The three forms now available – transdermal patches, chewing gum and nasal spray – deliver nicotine at different rates and to different levels. Therefore, it might be expected that smokers with different characteristics, and at different levels of nicotine dependence, will be helped more by one or other method.*

Aim. *The aim of the study was to examine whether the effectiveness of transdermal patches is related to nicotine dependence or to other smoker characteristics and to investigate factors predicting smoking cessation using patches.*

Method. *Data from a randomized, double-blind, placebo-controlled trial of nicotine transdermal patches were analysed retrospectively. The trial, conducted in 1990–1992, involved 1686 patients recruited from 19 general practices in Oxfordshire. The main outcome measure was continuous smoking cessation from 8 to 52 weeks after the start of patch use, biochemically validated at 12, 24 and 52 weeks. The effectiveness of the patches was measured by the relative odds of sustained cessation using nicotine patches compared with placebo patches.*

Results. *Nicotine transdermal patches were more effective in smokers with moderate nicotine dependence [odds ratio (OR) 1.94; 95% confidence interval (CI) 1.24 – 3.04] than in mildly or highly dependent smokers (OR 0.98; 95% CI 0.58 – 1.65) (difference in ORs P<0.05) and more effective in those aged 24–49 years (OR 1.89; 95% CI 1.24 – 2.87) than in older smokers aged 50–65 years (OR 0.88; 95% CI 0.49 – 1.59) (difference in ORs P<0.05). Abstinence from smoking in the first week of the trial was the strongest predictor of sustained cessation and was more common among smokers using nicotine patches than those using placebo patches (33% of 842 compared with 22% of 844; P<0.001). Of first-week abstainers, 25 and 28% of 277 and 182 in the nicotine and placebo groups, respectively, achieved sustained cessation compared with 4% of 565 and 2% of 662 first-week smokers.*

Conclusion. *Nicotine transdermal patches were most effective for smokers with moderate nicotine dependence and for younger smokers. Early abstinence from smoking was the strongest predictor of sustained cessation. A week's trial of the patch proceeding to longer term use if abstinence is achieved may be an effective policy.*

Keywords: randomized trial; nicotine dependence; smoking cessation.

Introduction

IT has been reported from observational studies and randomized trials that smokers who are successful in giving up smoking tend to be highly motivated,[1-3] in an older age group,[1,3,4-7] well educated,[6-8] married or living with a partner,[2,3] and of high socioeconomic status.[1,5,8] Factors that work against successful quitting are heavy smoking,[5,6,8,9] high nicotine dependence[1,10] and living with (or spending much time among) other smokers.[1,2,6] Although some of these associations are uncertain, that between heavy smoking and difficulty in stopping has persistently been reported.[11]

Three overviews of randomized controlled trials have confirmed that the likelihood of giving up smoking can be increased by nicotine replacement therapy, in the form of transdermal patches[12-14] or chewing gum.[13,14] Results vary between trials, but smokers using either of these aids have a cessation rate that is 1.5–2 times that achieved on placebo treatment.[13] A slightly greater degree of benefit was reported in the only published randomized trial of a nicotine nasal spray.[15]

The rationale behind nicotine replacement therapy is that nicotine is the addictive substance in tobacco, and its withdrawal causes a range of unpleasant symptoms after smoking cessation.[16,17] The three available forms of therapy work in different ways. Nicotine chewing gum and nicotine nasal spray can be used at will, depending on the degree of craving and other symptoms. They both produce rapid surges in plasma nicotine concentration,[15,18] and with repeated use, can achieve a plasma nicotine concentration that is about two thirds of the peak level produced by cigarette smoking.[15,18,19] However, a nicotine transdermal patch is applied each morning, and the steady dose of nicotine that it supplies cannot be adjusted by the user. After some hours, a plateau level of plasma nicotine concentration is achieved, similar to the trough levels experienced by a moderate to heavy smoker.[17]

Therefore, there are biologically plausible reasons for believing that smokers with different levels of nicotine dependence will be helped more by one or other method of nicotine replacement therapy. In practice, nicotine chewing gum appears to work best for smokers who are highly nicotine dependent. In six randomized trials of 2 mg nicotine gum, analysis by nicotine dependence showed that the gum was effective (compared with placebo gum) in highly dependent subjects but was generally ineffective in subjects with low nicotine dependence.[14] In the only trial

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of nicotine nasal spray, the spray also tended to be more effective in those with high nicotine dependence than in those of lower nicotine dependence.[15] In contrast, in the only patch trial giving information on nicotine dependence, patches appeared to be most effective in the middle range of dependence, and less effective in both the highly dependent and the least dependent smokers.[20] However, this result, relating to smoking abstinence at 3 months, was based on a small number of subjects. Whether the effectiveness of nicotine transdermal patches is modified by characteristics other than nicotine dependence has never been examined.

A recent observational study based on nearly 1500 smokers motivated to give up smoking using nicotine patches identified factors that were associated with successful cessation.[3] These included being aged 40 years or more, male sex, living with a spouse or partner and being highly motivated to quit. However, because there was no control group, it was impossible to determine to what extent these characteristics would have been associated with successful cessation even without nicotine replacement.

It would be useful to be able to identify at the start of any treatment programme those smokers who are most likely to benefit from nicotine transdermal patches (and those for whom patches are unlikely to be beneficial). A large randomized controlled trial of the use of nicotine transdermal patches in general practice carried out by the Imperial Cancer Research Fund General Practice Research Group[21,22] allowed this question to be addressed by comparing cessation rates in the nicotine and placebo groups for subjects with different characteristics. The study set out first to test the hypothesis that nicotine patches are most effective in smokers who are moderately dependent on nicotine and least effective in mildly and highly dependent smokers, and secondly, to examine whether the effectiveness of nicotine transdermal patches is related to other easily identified smoker characteristics.

Method

Randomized trial

A double-blind, placebo-controlled, randomized trial was carried out in 19 practices in Oxfordshire in 1990–1992. Detailed methods and results have already been reported.[21,22] In summary, 1686 heavy smokers (smoking 15 or more cigarettes a day) aged 24–65 years were randomly assigned to one of four groups: to receive nicotine transdermal patches or placebo patches with a specially designed booklet of support material or a standard Health Education Authority leaflet. Nicotinell® TTS patches (Zyma), in reducing sizes, were used over 12 weeks. Subjects were reviewed by a trial nurse at 1, 4, 8, 12, 24 and 52 weeks.

Definition of sustained smoking cessation

Sustained smoking cessation refers to reported continuous cessation from 8 to 52 weeks, biochemically confirmed at 12, 24 and 52 weeks. Confirmation was by a salivary cotinine concentration $\leqslant 113.5$ nmol l^{-1} (20 ng ml^{-1})[23] in most cases (227 of 263 abstainers confirmed at 12 weeks; 165 of 180 confirmed at 24 weeks; and 143 of 156 confirmed at 52 weeks). For the remaining minority, confirmation was by an exhaled carbon monoxide reading of $\leqslant 10$ parts per million (ppm).[24] Subjects who failed to attend for review were assumed to be smokers.

Smoker characteristics

The baseline smokers' characteristics for which data were available were: age, sex, nicotine dependence, whether or not the first cigarette was smoked within 30 min of waking, and number of cigarettes smoked per day. Nicotine dependence was assessed by the modified Horn–Russell score[25] (Appendix 1). Abstinence from smoking during the first week of the trial (confirmed by an exhaled carbon monoxide reading of $\leqslant 10$ ppm) was also considered in the analysis. This factor can be considered both as a predictor of sustained smoking cessation and as an intermediate outcome. Unlike the other factors considered, it was not independent of the trial group.

To clarify interpretation of the results, continuous variables were grouped into categories. The boundaries were chosen so as to cut off, as nearly as possible, the highest or lowest quarters of the distribution, or both, and to be clinically relevant. The groups used were as follows: age, 24–49 and 50–65 years; nicotine dependence score, low 0–11, moderate 12–18 and high 19–27; and number of cigarettes per day, 15–19, 20–29, 30+. There were three missing values: number of cigarettes smoked per day (one subject) and whether or not the first cigarette was smoked within 30 min of waking (two subjects).

Statistical analysis

The relative odds (odds ratio) of sustained cessation associated with the use of nicotine patches compared with placebo were estimated by logistic regression. To test whether the odds ratios were different for smokers with different levels of a particular baseline characteristic, the presence of a statistically significant interaction between that characteristic and treatment (nicotine or placebo) was tested for in a logistic regression model. In these analyses, smoker characteristics were classified into two levels only: dependence as moderate (score of 12–18) or not moderate (all other scores); and cigarettes per day as moderate (15–29) or high (30 or more). Interactions were entered after the main effects of all other baseline characteristics had been fitted. Significance levels were based on the likelihood ratio test. All significance tests were two-tailed.

Results

Sustained smoking cessation over one year was achieved by 10.8% of the 842 subjects randomized to use nicotine patches and by 7.7% of the 844 subjects randomized to use placebo patches.

Baseline characteristics associated with sustained smoking cessation in placebo group

The proportion of subjects achieving sustained smoking cessation in the placebo group, according to different smoker characteristics, is shown in Table 1. The only characteristic identifiable at the start of the trial that was significantly associated with sustained cessation was older age (50–65 years). Of 217 subjects in this older age group, 12.9% achieved sustained cessation compared with 5.9% of 627 younger smokers [difference 7.0%; 95% confidence interval (CI) 2.2 – 11.8; $P < 0.01$]. Sustained smoking cessation tended to be more common among subjects with low levels of nicotine dependence than among subjects with higher levels of dependence, and more common among lighter than heavier smokers, but these associations were not statistically significant. Logistic regression analysis confirmed that older age (50–65 years) was significantly associated with smoking cessation ($P < 0.01$) after adjusting for all other baseline characteristics.

Baseline characteristics associated with sustained smoking cessation in nicotine group

Table 1 shows the proportion of subjects achieving sustained smoking cessation in the nicotine group, according to different

smoker characteristics. In contrast to the placebo group, age was not associated with sustained cessation, but dependence score was so associated ($P<0.05$), the greatest proportion of successful quitters being among moderately dependent smokers. In a logistic regression, dependence score was a statistically significant predictor of smoking cessation ($P<0.01$) after allowing for all other baseline characteristics.

Effectiveness of nicotine patches in subjects with different baseline characteristics

The odds ratio gives the odds of sustained cessation using the nicotine patch compared with the placebo, and thus, is a measure of the effectiveness of nicotine patches. For the entire sample, the odds ratio (adjusted for baseline smoker characteristics) was 1.48 (Table 1). Comparison of odds ratios for complementary groups showed that the nicotine patch was more effective ($P < 0.05$) for subjects aged 24–49 years (odds ratio (OR) 1.89) than for those aged 50–65 years (OR 0.88), and more effective ($P<0.05$) for subjects who were moderately nicotine dependent (OR 1.94) than for the mildly or highly dependent (OR 0.98, 95% CI 0.58 – 1.65). There was a tendency for nicotine patches to be more effective for those smoking 30 or more cigarettes a day (OR 2.44) than for lighter smokers (OR 1.26, 95% CI 0.86 – 1.85).

Abstinence from smoking in first week of trial

Abstinence from smoking in the first week of the trial was achieved by 32.9% of the 842 subjects in the group using nicotine patches compared with 21.6% of the 844 subjects in the placebo group, a difference of 11.3% (95% CI 7.1 – 15.5; $P<0.001$). First-week abstinence was by far the strongest predictor of sustained smoking cessation. Of first-week abstainers, 24.9% of 277 subjects in the group using nicotine patches and 28.0% of 182 subjects in the placebo group achieved sustained cessation, compared with only 3.9% of 565 and 2.1% of 662 first-week smokers (difference between first-week smokers and abstainers $P<0.001$ in each case).

For first-week abstainers, the odds ratio of sustained smoking cessation among those using nicotine patches compared with placebo (after adjustment for baseline characteristics) was 0.92 (95% CI 0.60 – 1.43); for first-week smokers it was 1.93 (95% CI 0.98 – 3.80). Thus, the effect of the patch resulted partly from an increase in the rate of first-week abstinence and partly from an increase in the rate of longer term abstinence among smokers who failed to give up in the first week.

Table 1. Sustained smoking cessation by baseline characteristics in groups randomized to receive nicotine transdermal patches and placebo patches.

Baseline characteristic	% of subjects with characteristic achieving sustained cessation in: Placebo group	Nicotine group	Adjusted OR[a] (95% CI)
Total (n = 844/842)	*7.7*	*10.8*	1.48 (1.06 – 2.07)
Age (years)			
24–49 (n = 627/640)	*5.9*	*10.6*	1.89 (1.24 – 2.87)
50–65 (n = 217/202)	*12.9**	*11.4*	0.88 (0.49 – 1.59)
Sex			
Women (n = 480/449)	*7.9*	*10.0*	1.32 (0.84 – 2.08)
Men (n = 364/393)	*7.4*	*11.7*	1.63 (0.99 – 2.69)
Nicotine dependence score[b]			
Low (n = 213/213)	*8.9*	*8.5***	0.90 (0.46 – 1.77)
Moderate (n = 437/435)	*7.8*	*13.8*	1.94 (1.24 – 3.04)
High (n = 194/194)	*6.2*	*6.7*	1.12 (0.50 – 2.54)
Time of 1st daily cigarette			
30+ minutes after waking (n = 216/203)	*8.8*	*12.8*	1.58 (0.84 – 2.95)
<30 minutes after waking (n = 627/638)	*7.3*	*10.2*	1.43 (0.96 – 2.12)
No. of cigarettes smoked daily			
15–19 (n = 138/145)	*11.6*	*10.3*	0.94 (0.44 – 2.00)
20–29 (n = 515/485)	*7.4*	*9.9*	1.39 (0.89 – 2.17)
30+ (n = 190/212)	*5.8*	*13.2*	2.44 (1.17 – 5.09)

n = number of subjects with characteristics in placebo group/nicotine group. OR = odds ratio. CI = confidence interval. [a]Odds of sustained cessation when using the nicotine patch compared with the placebo patch, after adjustment for all other baseline variables. [b]See Appendix 1 for details: low = score of 0–11, moderate = 12–18 and high = 19–27. *In placebo group, smoking cessation associated with age ($P<0.01$). **In nicotine group, smoking cessation associated with dependence score ($P<0.05$).

Discussion

Two studies have suggested that complete or almost complete abstinence from smoking in the early weeks of an attempt to quit is a powerful predictor of longer term success.[3,26] In the present study, the ability to refrain from smoking for at least a week was the strongest predictor of smoking cessation at one year. First-week abstinence among those using nicotine transdermal patches carried a one in four chance of long-term smoking cessation, but this rate dropped to one in 26 for those who smoked during the first week.

As a result of their findings, Kenford and colleagues suggested that clinicians should concentrate their efforts on helping smokers to remain abstinent for the first 2 weeks of treatment.[26] It is not clear that this approach would produce corresponding long-term benefits, since it might simply dilute the early-abstaining group with less motivated subjects. The results of the present study suggest some dilution effect, but not enough to cancel out the benefit of short-term abstinence. Those subjects randomly allocated to use nicotine patches had a much greater likelihood of refraining from smoking in the first week than those using placebo (33% of subjects compared with 22%), but given early abstinence, only a slightly lower chance of remaining abstinent for the whole year (25% of subjects compared with 28%). Thus, the proportion of subjects who were abstinent continuously from the first week for the whole year was 8% in the group using nicotine patches and 6% in the placebo group (difference 2%, 95% CI 0 – 5%).

Since it makes sense to offer treatment to those smokers with a reasonable chance of giving up, the results of the present study could help to determine policy regarding the use of nicotine patches. Nicotine patches, backed up by professional support, might be offered to motivated subjects for a week in the first instance. Those smokers refraining from smoking during that week could be encouraged to continue in the knowledge that they had a strong chance of longer term success. Since fewer than 4% of those who smoked in the first week achieved sustained cessation using patches, it would be much less effective to continue treatment in that group. This conclusion may appear paradoxical, since the first-week smokers were one of the subgroups who obtained the greatest relative benefit from the nicotine patch, with odds of quitting nearly twice that of subjects using the placebo patch. However, the absolute benefit (an improvement in cessation rate from 2 to 4% of subjects) was minimal because so few in this category were successful in quitting.

Are nicotine patches likely to confer the same degree of benefit on all types of smoker or can people be identified who are

likely to do particularly well (or badly) using such patches? Abelin and colleagues, in an earlier small trial of transdermal nicotine patches, reported that, at 3 months, smokers at both extremes of the dependence scale appeared to show little if any benefit from patches, but those with moderate nicotine dependence showed considerable benefit.[20] The results at one year from the present study support this observation. Nicotine patches were clearly effective for subjects with moderate nicotine dependence (the central half of the sample), but not effective for those with either low or high dependence. In apparent contrast, Stapleton and colleagues, in a retrospective analysis of data from a randomized controlled trial, reported no interaction between nicotine dependence and the effectiveness of patches.[27] However, that study sought a linear or curvilinear relationship between effectiveness and dependence, and thus, could have missed the particular relationship that we observed, in which moderate dependence contrasted with both high and low dependence. It is recognized that retrospective analyses of this sort are sensitive to the choice of variables entered into the model, and to the measurement scales used, and it is possible that the result in the present study may be caused by chance. Nevertheless, it seems reasonable to suggest that the steady but relatively low level of nicotine that the patch provides may not satisfy the craving of the most highly dependent smoker. For such smokers, additional support from nicotine chewing gum or a nasal spray may be helpful. Conversely, for the least dependent smoker, it may be that nicotine replacement (in any form) is irrelevant.

In this study, there was also a statistically significant interaction between patch effectiveness and age. Nicotine patches were more effective among younger subjects (those aged 24–49 years) than among older subjects (aged 50–65 years), 13% of whom were able to achieve sustained cessation using the placebo patch. The results also suggest that nicotine patches might be more effective for heavy smokers (those smoking 30 or more cigarettes a day) than for lighter smokers. Although heavier smokers tended to be more nicotine dependent, the results showed that these two measures were by no means interchangeable. All these observations provide hypotheses for further testing.

The trial has shown clearly that transdermal nicotine patches can help to maintain abstinence from smoking in the first days after giving up, and that this early abstinence is important for long-term success. Smokers with moderate nicotine dependence, younger smokers and those who smoke heavily are likely to gain particular benefit from use of transdermal nicotine patches.

Appendix 1. Modified Horn–Russell questionnaire.

Score each question on a scale of 0 (not at all) to 3. Total score 0–27.

1. I get a definite craving to smoke when I have to stop for a while.
2. I light up a cigarette without realizing I still have one burning in the ash tray.
3. I smoke automatically without even being aware of it.
4. When I have run out of cigarettes, I find it almost unbearable until I can get them.
5. I find it difficult to go as long as an hour without smoking.
6. I find myself smoking without remembering lighting up.
7. I get a real gnawing hunger to smoke when I haven't smoked for a while.
8. I am very much aware of the fact when I am not smoking.
9. I would find it difficult to go without smoking as long as a week.

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