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ORIGINAL INVESTIGATION

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A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler

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Abstract *Rationale:* Nicotine replacement therapy (NRT) in varying forms is becoming widely used. Clinicians, therapists and regulatory authorities are interested in the abuse liability and dependence potential of the different forms. *Objectives:* To compare the abuse liability and dependence potential of nicotine gum, transdermal patch, spray and inhaler. *Methods:* 504 male and female smokers seeking help with stopping smoking were randomly allocated to the four products. Measures were taken at the designated quit date, then 1 week, 4 weeks, 12 weeks and 15 weeks later. Smokers were advised to use the product for up to 12 weeks. Those still using the product at the 12-week visit were advised to cease use by week 14. Measures included: pleasantness and satisfaction ratings at weeks 1 and 4 (used as a marker of abuse liability); ratings of feeling dependent on NRT at weeks 1, 4, 12 and 15 (used as a marker of subjective dependence); mood and physical symptoms ratings at weeks 12 and 15 (the change being used to assess physical dependence on NRT), continued usage of NRT at week 15 (used as an marker of behavioural dependence). *Results:* Average ratings of pleasantness were low. The nicotine patch was rated as less unpleasant to use than all other products. There were no significant differences between the products in terms of satisfaction or subjective dependence except at week 15 when no patch users rated themselves as dependent. Continued use of NRT at week 15 was related to rate of delivery of nicotine from the products – 2% for patch, 7% for gum and inhaler, 10% for spray ($P<0.05$ for linear association). Among those abstinent for 15 weeks, the figures were: 8%, 25% and 37%, respectively. Stopping NRT use between weeks 12 and 15 was not accompanied by withdrawal discomfort or increased frequency of urges to smoke although subjects stopping inhaler use experienced a mild increase in strength of urges to smoke. We conclude that abuse liability from all four NRT products was low. Subjective dependence was moderate and did not differ across products. Behavioural dependence was modest and was positively related to rate of nicotine delivery. Physicians can reassure their patients that most are able to come off NRT as recommended without discomfort.

Key words Nicotine replacement therapy · Dependence · Abuse liability

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Introduction

A majority of smokers are dependent on nicotine (USDHHS 1988). Nicotine replacement therapies (NRT) are designed to help wean smokers off nicotine and in clinical trials they typically double smokers chances of stopping smoking and staying off cigarettes for at least a year (Tang et al. 1994; Silagy et al. 1999). Pharmaceutical licensing authorities address both the efficacy and safety of drugs. As part of this, in the case of NRT, they consider the abuse liability and dependence potential of particular products. Similarly, doctors and other health professionals need to be equipped to address patient concerns regarding the risk of dependence on different types of NRT. Abuse liability concerns the extent to which the product will be used for other than therapeutic purposes. Dependence potential refers to the extent to which users become subjectively, physically or behaviourally dependent (see below).

The abuse liability and dependence potential of NRT products appears to be substantially less than that of cigarettes and it has been argued that this is because of slower absorption of nicotine (Henningfield and Keenan 1993; Hughes 1998).

Abuse liability can be assessed by examining the extent to which the product is attractive to users for reasons other than its therapeutic efficacy. This may be gauged by how far the product serves the psychological needs of users or is liked by users. Dependence potential can be assessed in several ways. One is to examine onset of withdrawal symptoms on termination of use (sometimes referred to as "physical dependence"). For example, West and Russell (1985a) found that long term-nicotine gum users reported mood and physical symptoms similar to those reported during smoking abstinence when their gum use was terminated. Another is by examining the proportion of users who feel dependent on a product ("subjective dependence"), and a third is the proportion of users who continue use beyond its recommended time-window (which may be construed as a marker of "behavioural dependence").

The products are targeted at smokers wishing to stop smoking, so it makes sense to examine abuse liability and dependence potential in that group. Previous research has indicated that the gum and nicotine nasal spray are both used beyond the recommended 12-week period by some smokers trying to stop (e.g. Hajek et al. 1988; Hughes et al. 1991; Sutherland et al. 1992). However, in those studies, smokers continued to receive the products free of charge as part of the study if they wanted it. Data are needed from situations as close to the "real world" as possible. Information is also lacking on relative dependence potential and abuse liability of the range of nicotine replacement products currently available. In particular, information is needed on the dependence potential and abuse liability of the nicotine inhaler which is a relatively new product and delivers nicotine at a rate similar to that from 2 mg nicotine gum but involves behaviours similar to those involved in cigarette smoking (e.g. Hajek et al. 1989; Leischow et al. 1996).

We carried out a study comparing Nicorette gum, 15 mg 16-h Nicorette patch, Nicorette nasal spray and Nicorette Inhalator in terms of: preference, withdrawal symptom relief, efficacy in terms of 12-week abstinence rate, usage patterns, acceptability, abuse liability and dependence potential. This paper reports on the abuse liability and dependence potential of the products. Abuse liability and dependence potential were construed as described above.

Materials and methods

In a randomised controlled trial, 504 smokers seeking help with stopping smoking were assigned to receive one of four NRT products:

1. Nicorette gum – 2 mg or 4 mg (*n*=127)
2. Nicorette transdermal patch – 15 mg, 16-h (*n*=124)
3. Nicorette nasal spray (*n*=126)
4. Nicorette inhaler (*n*=127)

Further details of participants and methods are given in Hajek et al. (1999). Smokers were eligible for inclusion if they were at least 18 years old, had smoked an average of ten or more cigarettes per day, were motivated to stop smoking, were generally in good health, were not currently receiving treatment for a psychiatric disorder, had not tried to stop smoking using NRT within the past 3 months, and for whom none of the four NRT products was contraindicated. Written informed consent was obtained once the study procedures had been explained to the smokers. The study was approved by the ethics committees of the District Health Authorities of the two sites.

The participants agreed to take part in the study knowing that they might be allocated to any one of these products. They were also aware that they would have to purchase the products at approximately half the normal retail price (£7 for 105 pieces of gum, seven patches, one bottle of nasal spray solution giving 200 1-mg doses or 42 inhaler cartridges). The reason for this was to mimic as far as possible the conditions in countries such as the UK where NRT is not currently reimbursable.

Participants were scheduled to attend on five occasions:

Session 1:	Week 0	Designated quit date
Session 2:	Week 1	One week after quit date
Session 3:	Week 4	Four weeks after quit date
Session 4:	Week 12	Twelve weeks after quit date – only those abstinent at session 3 were invited
Session 5:	Week 15	Fifteen weeks after quit date – only those abstinent at session 4 were invited

In order to standardise information given to participants, they were instructed about all the NRT products and their own product in particular by means of a video presentation. Brief advice on how to maximise the chances of stopping smoking and remain abstinent was given at each session. Participants were invited to use the NRT product to which they had been assigned according to the manufacturer's instructions for up to 12 weeks. At the week 12 visit, participants who were still using NRT were asked to cease use within 2 weeks (week 14) by means of a reduction regimen. Participants were supplied with NRT at each visit in quantities requested.

Measures were taken as follows:

1. The amount of product used since the last visit was recorded at each visit. This was measured in "units" (given that the dosing forms were very different). For the gum, a unit was one piece. For the patch, a unit was one patch. For the nasal spray, it was one application. For the inhalator, a unit was one cartridge.
2. Abstinence from cigarettes was reported and verified by expired-air carbon (<10 ppm) monoxide concentrations at each session.
3. At session 2 (1 week post-quit date) and 3 (4 weeks post-quit date), participants rated the NRT pleasantness/unpleasantness and satisfaction compared with their usual cigarettes using a 9-point scale, 1=very unpleasant/unsatisfying, 5=neutral, 9=very pleasant/satisfying (used to index abuse liability).
4. At sessions 2, 3, 4 and 5, participants rated how dependent they felt on their product, 1=definitely not, 2=possibly, 3=probably, 4=definitely (used to index subjective dependence).
5. At all sessions, participants completed the mood and physical symptoms scale and ratings of difficulty not smoking and strength and duration of urges to smoke (West and Russell 1985b). This paper reports on findings from sessions 4 and 5 (used to index physical dependence).
6. At session 5, the proportion of participants still using their product was recorded (used to index behavioural dependence).

Product ratings are reported for participants who attended the session in question, used at least one unit of their NRT product per week and were abstinent from cigarettes. Given that participants in smoking cessation trials tend to drop out if they resume smoking, the numbers declined over the course of the study. The reasons for limiting analyses of subjective ratings to users of NRT who were abstinent from smoking were: non-abstainers would not be in a position to become dependent, their product ratings could be biased in order to justify failure of their attempt to stop smok-

ing, and their consumption would be affected by the fact that most of them would be terminating their NRT use shortly after returning to smoking.

Results

Table 1 shows the percentages of participants who used at least one unit of NRT per week since the previous visit (except for week 15 when the figure refers to the preceding week only, by when participants should have ceased NRT use). There were no significant differences between the groups except at week 15. Coding the NRT products according to their rate of nicotine delivery (1=patch, 2=gum and inhaler, 3=spray), there was a significant linear association between rate of NRT delivery and prevalence of use at week 15 (Mantel-Haenszel=6.2, P=0.01).

There was no significant difference between the groups in terms of abstinence rates at any time point (Hajek et al. 1999). Thus, at week 1 the proportion who had been continuously abstinent on the different products were: gum 50%, patch 55%, nasal spray 54% and inhalator 43%; at week 4 the proportion who had been continuously abstinent on the different products were: gum 31%, patch 36%, nasal spray 38% and inhalator 35%; at week 12 the proportion who had been continuously abstinent on the different products were: gum 20%, patch 21%, nasal spray 24% and inhalator 24% (Hajek et al. 1999). Table 2 gives the percentages of smokers who used at least one unit of NRT per week and had abstained from cigarettes. There were no significant differences between the groups at any time point.

Table 3 shows the percentages of participants who used NRT but were not abstinent from cigarettes at each visit. There were no significant differences between the groups. It is clear that a substantial proportion of participants in all groups used NRT as well cigarettes but that this number declined over the course of the study.

Table 4 shows the average daily usage of NRT products among those who used them and were abstinent. The weekly usage dropped significantly over the course of the study. A comparison of NRT usage over time among for the core sample of participants who were abstinent up to week 12 also showed a significant drop over time (F=33.2, P<0.001).

Figure 1 shows the mean pleasantness ratings after the first week of NRT use among those who abstained from cigarettes and used at least one item of NRT in that week. The ratings were modest. Analysis of variance with post-hoc pairwise comparisons by Scheffe's test indicated that the patch was rated as less unpleasant than the other types of NRT (P<0.05). The figure also shows the satisfaction ratings. There were no significant differences between the products.

Table 1 Percentage (n) of participants who used at least one unit of NRT per week at each session (base: all smokers)

	Gum[a]	Patch	Spray	Inhaler
Week 1	82 (104)	86 (107)	83 (104)	76 (97)
Week 4	52 (66)	65 (80)	52 (65)	54 (68)
Week 12	24 (30)	22 (27)	32 (40)	31 (39)
Week 15	7 (9)	2 (3)	10 (13)	7 (9)

[a] Participants were offered 4 mg gum if using more than ten pieces of 2 mg gum per day in the previous week; six subjects chose 4 mg gum at week 1, with three using at week 4 and one at week 12

Table 2 Percentage (n) of participants who were abstinent and using at least one unit of NRT per week at each session (base: all smokers)

	Gum	Patch	Spray	Inhaler
Week 1	50 (64)	55 (68)	54 (68)	43 (54)
Week 4	35 (44)	42 (52)	37 (47)	41 (52)
Week 12	20 (25)	14 (17)	25 (32)	24 (30)
Week 15	7 (9)	2 (3)	8 (10)	7 (9)

Table 3 Percentage (n) of participants who were not abstinent from cigarettes but used at least one unit of NRT per week at each session (base: all smokers)

	Gum	Patch	Spray	Inhaler
Week 1	32 (40)	32 (39)	29 (36)	34 (43)
Week 4	17 (22)	23 (28)	14 (18)	13 (16)
Week 12	4 (5)	8 (10)	6 (8)	7 (9)
Week 15	0 (0)	0 (0)	2 (3)	0 (0)

Table 4 Average (SD) units of NRT used per day by people abstinent from cigarettes and using at least one unit of NRT per week at each session (see Table 2 for sample sizes). One unit=one piece of gum, one patch, one "shot" of nasal spray in one nostril or one cartridge of inhalator

	Gum	Patch	Spray	Inhaler
Week 1	9.5 (3.0)	1.0 (0.2)	24.5 (11.2)	4.3 (1.9)
Week 4	6.6 (2.7)	0.6 (1.8)	17.5 (7.5)	2.6 (1.6)
Week 12	5.6 (3.8)	0.6 (0.3)	20.1 (11.8)	2.4 (1.7)
Week 15	2.5 (2.6)	0.3 (0.2)	4.8 (4.0)	1.0 (1.3)

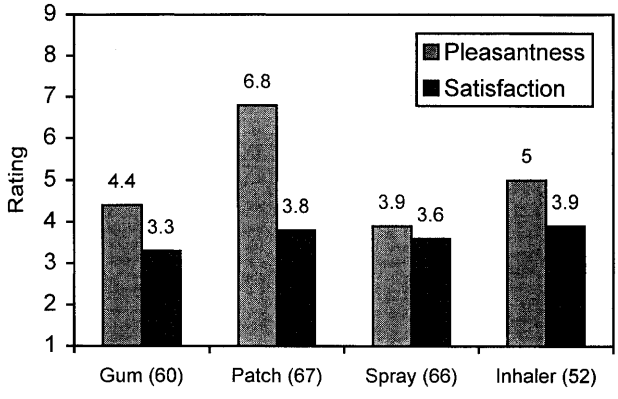

Fig. 1 Mean pleasantness and satisfaction ratings at week 1 among those using at least one unit of NRT in that week (bases are given in *brackets*)

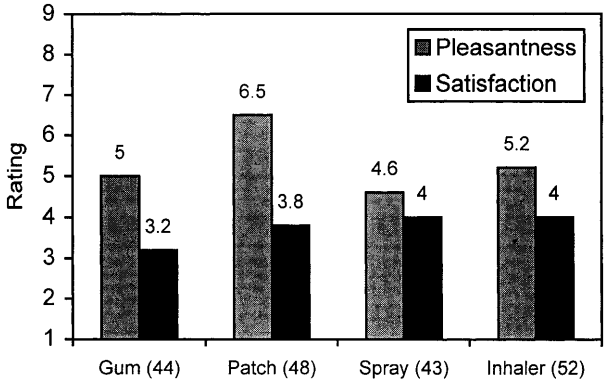

Fig. 2 Mean pleasantness and satisfaction ratings at week 4 among those using at least one unit of NRT per week (bases are given in *brackets*)

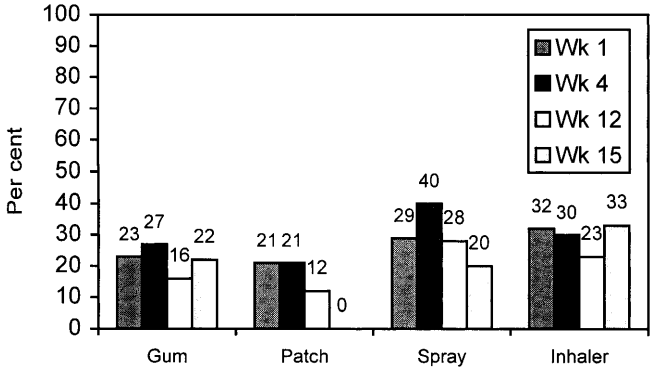

Fig. 3 Percentages of participants who reported feeling "probably" or "definitely" dependent on their NRT product (bases are different for each week; see Table 2)

Figure 2 shows the corresponding ratings at the week 4 assessment. Again the ratings were modest. The patch was rated as less unpleasant than all the other products ($P<0.05$ by Scheffe's test). Figure 3 shows the perceived dependence at weeks 1, 4, 12, and 15. Overall, approximately one quarter of participants felt that they were probably or definitely dependent on their product. Although it appears that at weeks 4 and 12, ratings were higher among the smokers using nasal spray, the differences were not statistically significant. At week 15, none of the patch users felt dependent.

Figure 4 shows the percentage of those who had been abstinent from cigarettes and using each product up to and including week 12 who were still using it at week 15, despite advice to stop. The lowest continued use was among those on the patch and the highest on the nasal spray (using the coding system described above for rate of nicotine delivery of NRT products, Mantel-Haenszel= 6.5, $P=0.01$).

The difference between the usage rates at week 15 in Fig. 4 and Table 1 reflects the fact that Fig. 4 is limited to participants who were abstinent for 12 weeks and used NRT for that period.

Table 5 shows the changes in withdrawal ratings in successful abstainers who were using their NRT at week 12 and ceased the use by week 15. There were no significant changes over time, except that time spent with urges to smoke decreased and the NRT groups differed in changes in strength of urges to smoke, with a slight increase in the inhaler group versus a decline in the other groups.

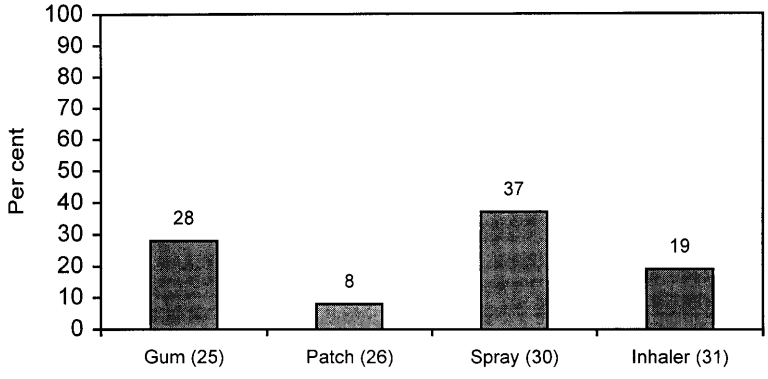

Fig. 4 Percentage of those abstinent and using NRT from quit date to week 12 who were still using at week 15 (bases are given in *brackets*)

Table 5 Mean (SD) changes in ratings of mood and physical symptoms and urges to smoke before and after termination of NRT use (weeks 12–15). Figures are ratings for week 15 visit minus ratings for week 12 visit. Positive number indicates an increase and negative number indicates a decrease. Base is patients continuously abstinent from cigarettes up to week 15 who were using NRT at week 12 and not using NRT at week 15 (n=48)

	Gum(n=10)	Patch(n=12)	Spray(n=11)	Inhaler(n=15)
Depression	0.3 (0.7)	–0.1 (0.7)	–0.3 (0.6)	–0.1 (1.0)
Irritability	0.3 (0.7)	0.0 (1.0)	–0.1 (1.0)	0.3 (1.1)
Restlessness	–0.3 (1.1)	–0.1 (1.0)	0.2 (0.8)	0.0 (0.6)
Hunger	–0.2 (0.58)	–0.4 (1.22)	0.1 (1.10)	0.1 (1.05)
Poor concentration	0.14 (0.77)	0.18 (0.95)	0.0 (0.68)	–0.2 (0.98)
Difficulty not smoking	–0.2 (0.70)	0.0 (1.06)	–0.3 (0.70)	0.1 (1.05)
Strength of urges[a]	–0.1 (0.47)	–0.1 (0.70)	–0.3 (0.46)	0.4 (1.02)
Time spent with urges[b]	–0.4 (0.93)	–0.3 (0.85)	–0.4 (0.63)	–0.3 (1.33)

[a] Significant difference between NRT types by analysis of variance $F=3.0$, $P<0.05$
[b] Significant decrease over time, $F=7.0$, $P<0.05$

Discussion

The results suggest that the abuse liability of the NRT products examined is low. On average, the products were rated neither pleasant nor unpleasant even by smokers who were relying on them to help them stay off cigarettes. The NRT products were not rated as satisfying and there was little difference between them in this regard. Participants did report feelings of subjective dependence on the products although there was no evidence that products differed in this. Behavioural dependence was related to rate of nicotine delivery from the product.

The lack of pleasantness of the gum, inhaler and nasal spray is probably due to irritation in the mouth, throat and nose. Any positive nicotine effects appear to be masked by these superficial features of use. Thus the patch, which had a very slow rate of nicotine delivery but was easy to use, was rated as more pleasant than the other products.

The relationship between rapidity of nicotine delivery from the products and behavioural dependence potential is what would be expected from Henningfield et al.'s (1993) pharmacological model of nicotine dependence. This view has also been proposed by other authors (e.g. Foulds 1999). The fact that the inhalator, with its similarity to cigarettes in terms of behaviour involved in its use, had a similar dependence potential to the nicotine gum, also supports this simple pharmacological model; the manipulation and puffing behaviour and simulation of the "scratch" in the throat provided by cigarettes did not lead to greater dependence.

There was no evidence of withdrawal discomfort on termination of NRT use, although termination of inhaler use was associated with an increase in strength of urges to smoke. However, there was no corresponding increase in other ratings and considering the number of comparisons made, this may have been a chance finding. Other authors (see Hughes 1998) have found some evidence of withdrawal discomfort on cessation of NRT use, but this was in a small minority of smokers who had been unable to terminate nicotine gum use after 1 year.

Several factors should be taken into account when interpreting these findings. First of all, the sample was limited to smokers seeking help with stopping. Among smokers who buy NRT products but do not seek formal treatment, NRT use and prevalence of behavioural dependence are likely to be lower. Secondly, we only followed NRT users for 1 week, after they were supposed to stop using the products; far fewer smokers would be expected to continue using the products in the long term. It may be noted also that average consumption among users at week 15 was much lower than at week 12. While the nature of the sample and the short-follow-up may overestimate the real-world dependence potential of the NRT products as a whole, it is unlikely that they would affect estimates of their comparative dependence potential.

Patients worried about becoming dependent on NRT and asking advice regarding the dependence potential of different NRT products can be reassured that most people manage to stop using NRT at the end of the prescribed course without discomfort. It should also be noted that long term use of NRT is acknowledged as being considerably safer than smoking so if it comes to choice between continuing to smoke and using NRT long term the latter would be preferable from a health perspective.

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