ORIGINAL RESEARCH ARTICLE

Drug Safety 1999 Jun; 20 (6): 545-555
0114-5916/99/0006-0545/$05.50/0

© Adis International Limited. All rights reserved.

Predictors and Timing of Adverse Experiences During Transdermal Nicotine Therapy

Steven G. Gourlay,[1,2] *Andrew Forbes,*[1] *Tracey Marriner*[1] and *John J. McNeil*[1]

1 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

2 Genentech Inc., South San Francisco & Departments of Epidemiology & Biostatistics and Medicine, University of California, San Francisco, California, USA

Abstract

Objectives: Difficulty sleeping is a recognised tobacco withdrawal symptom, but sleep problems, like application site reactions, are commonly reported as adverse reactions to transdermal nicotine therapy. However, no studies have examined potential predictive factors associated with the occurrence of expected adverse experiences during transdermal nicotine therapy. The subject of skin tolerability among patients with a history of eczema, psoriasis or other skin disorders is of particular interest, as are the relationships between plasma concentrations of nicotine, concurrent smoking, sleep problems and nausea.

Methods: The cohort study involving 1392 participants was designed to assess the timing, severity and predictive factors of adverse experiences reported during 24-hour transdermal nicotine therapy. Data were collected on patients aged 18 to 70 years old who were smokers and who had expressed a strong desire to stop smoking. The intervention consisted of brief behavioural counselling, a booklet containing smoking cessation advice and instructions for use of the patches, and a 12-week course of decreasing transdermal nicotine doses.

Results: Follow-up was available on 1392 out of 1481 study participants. The majority of adverse experiences were mild. Sleep problems occurred in 669 out of 1392 (48%) participants and most often commenced on the day of smoking cessation. Application site reactions occurred in 478 out of 1392 (34%) participants and most often occurred after 6 days of therapy. No predictor had an adjusted hazard ratio above 2. Statistically significant ($p < 0.05$) predictors of sleep problems were successfully quitting smoking and female gender. Predictors of application site reactions were psoriasis or eczema, other skin conditions, age <40 years, female gender, place of birth outside Australasia, and trade or university education level.

Substantially increased nicotine intake during therapy compared with baseline smoking occurred in 8% of participants who smoked concurrently, and 4% of participants who did not ($p = 0.1$). Increased nicotine intake was associated with a modest increase in the overall rate of adverse experiences (89% *vs* 63%, p =

0.04) and dizziness/lightheadedness (17% *vs* 3%, p = 0.03), but not with sleep problems or cardiovascular events.

Conclusions: Transdermal nicotine therapy appears to be well tolerated, even if the user smokes concurrently. Sleep disturbance during therapy appeared to be primarily associated with tobacco withdrawal rather than with nicotine excess from treatment with transdermal nicotine. Study participants with pre-existing skin disorders were somewhat more likely to report mild application site reactions than other participants.

Clinical trials of 24-hour transdermal nicotine therapy for smoking cessation report incidence rates of application site reactions ranging from 16 to 62% of users.[1-5] Rates of sleep problems range from 4 to 30%.[1-4,6-7] Other adverse experiences reported include dyspepsia, myalgia, cough[8] and nausea.[5] The vast majority of these adverse experiences are not severe and patients are able to continue therapy.

Despite being a common problem, no studies have examined potential predictive factors associated with the occurrence of expected adverse experiences during transdermal nicotine therapy. The subject of skin tolerability among patients with a history of eczema, psoriasis or other skin disorders is of particular interest, as are the relationships between plasma concentrations of nicotine, concurrent smoking, sleep problems and nausea.

This study describes the timing, severity and predictive factors of adverse experiences during 24-hour transdermal nicotine therapy for smoking cessation among a cohort of 1392 participants. The relationship of plasma nicotine concentrations to adverse experiences is explored to investigate their cause and the consequences of smoking while using transdermal nicotine therapy.

Study Participants and Methods

Details of the methodology of the first phase of the 'Another Good Attempt Involving Nicotine' (AGAIN) Study[9] and the plasma nicotine and cotinine measurement methods used[10] are published elsewhere. In brief, participants were aged 18 to 70 years, expressed a strong desire to quit smoking, had smoked 15 or more cigarettes daily for at least 3 years and were willing to consider a second serious quit attempt, should the first be unsuccessful (the AGAIN Study involved 2 quit attempts with transdermal nicotine, the first of which is described here).

The intervention consisted of brief behavioural counselling at each visit (baseline and weeks 1, 4, 8, 12 and 26), a booklet containing smoking cessation advice and instructions for use of the patches, and a 12-week course of decreasing transdermal nicotine doses.

The patches were active Nicotinell®/Habitrol® TTS (Ciba-Geigy Australia Ltd, Pendle Hill, Australia). Participants followed a fixed treatment regimen of one 21mg patch per 24 hours commencing from the quit date, changing to the 14mg per 24-hour dose after 4 weeks, to the 7mg per 24-hour dose after 8 weeks, and ceasing use at the end of 12 weeks. Participants were instructed to use each patch for 24 hours but were allowed to try removing the patches before bed if persistent sleep problems occurred. Application sites were alternated so that at least 3 days elapsed before a site was reused.

Exclusion Criteria

The exclusion criteria for the study were: medications that might interfere with tobacco withdrawal symptoms (i.e. regular use of other nicotine replacement products, β-blockers, clonidine, methyldopa, appetite suppressants, minor and major tranquillisers); pregnancy, lactation or potential pregnancy; significant mental or psychiatric illness; symptomatic ischaemic heart disease or cerebrovascular disease within the last 3 months; alcoholism; active malignancy; major medical disorders; and extensive skin lesions precluding

© Adis International Limited. All rights reserved.

patch application. Participants were instructed not to use other nicotine products during the study.

Adverse Experiences

Prior to the commencement of the study, during the process of gaining informed consent, potential adverse experiences were discussed with participants. All participants who attended 1 or more follow-up visits provided data about adverse experiences. Participants were asked about adverse experiences in response to a general question about well-being. Additionally, after the end of treatment, all contactable participants who had not returned for a scheduled visit were also asked if they had experienced a reaction to the patches that had caused permanent discontinuation of therapy. For participants with on-going adverse experiences possibly, probably or highly probably related to transdermal nicotine and who did not attend follow-up visits, detailed information was sought by telephone. Descriptions of adverse experiences were recorded in the case record forms by the research nurses and coded by study drug relationship (not related, unlikely, possible, probable or highly probable) and severity (mild, moderate or severe) at the same time.

Plasma Nicotine and Cotinine Measurements

Venous blood samples were taken from the first 1100 of 1481 participants and stored as frozen plasma. Blood samples were taken at the time of study visits, which were scheduled between 8am and 8pm. 500 plasma samples from the 1100 participants were randomly selected for laboratory analysis of nicotine and cotinine concentrations. Participants with undetectable concentrations of nicotine, or concentrations of cotinine <20 μg/L, were assumed to have violated the protocol (i.e. not smoking at baseline or not using transdermal nicotine at follow-up) and were excluded from the analyses involving plasma-concentration data.

Definitions

A 'possible' relationship between adverse experiences and transdermal nicotine treatment was defined by '. . . when the reaction follows a reasonable temporal sequence from administration of the drug; but could have been produced by the patient's clinical state or by other therapy. . .'. 'Probable' required observing a known response pattern to transdermal nicotine and confirmation by dis-

Table I. Number (%) of participants reporting application site reactions, sleep problems or musculoskeletal pain[a]

Adverse experience category	Total	Mild	Moderate	Severe	Unknown severity	Permanent treatment discontinuation	Temporary treatment interruption[b]
Any cutaneous application site reaction	478 (34.3)	314 (22.6)	127 (9.1)	36 (2.6)	1 (0.1)	57 (4.1)	56 (4)
erythema	205 (14.7)	141 (10.1)	51 (3.7)	13 (0.9)	0 (0)	24 (1.7)	25 (1.8)
rash	72 (5.2)	53 (3.8)	15 (1.1)	4 (0.3)	0 (0)	9 (0.6)	6 (0.5)
pruritus	289 (20.8)	200 (14.4)	71 (5.1)	18 (1.3)	0 (0)	34 (2.4)	33 (2.4)
irritation	65 (4.7)	41 (2.9)	15 (1.1)	8 (0.6)	1 (0.1)	9 (0.6)	9 (0.6)
vesicles	68 (4.9)	40 (2.9)	19 (1.4)	8 (0.6)	1 (0.1)	7 (0.5)	12 (0.9)
oedema	53 (3.8)	22 (1.6)	24 (1.7)	7 (0.5)	0 (0)	20 (1.4)	8 (0.6)
Musculoskeletal ache related to application sites	97 (7.0)	70 (5.0)	19 (1.4)	7 (0.5)	3 (0.1)	6 (0.5)	14 (1.0)
Any sleep problem	669 (48.1)	386 (27.7)	222 (16.0)	61 (4.4)	0 (0)	20 (1.6)	232 (16.7)
dreaming	414 (29.7)	253 (18.2)	127 (9.1)	34 (2.4)	0 (0)	9 (0.6)	105 (7.5)
other sleep disturbance	447 (32.1)	267 (19.2)	148 (10.6)	32 (2.3)	0 (0)	15 (1.1)	182 (13.1)

a All reports with possible, probable or highly probable relationship to the transdermal nicotine therapy. If participants reported an adverse experience more than once, the report with the maximum severity is counted. Denominator is all participants with adverse experiences follow-up (n = 1392).

b Includes participants removing patches at night only.

© Adis International Limited. All rights reserved.

continuation of therapy. 'Definite' required reappearance of the problem on repeat exposure. The severity of adverse experiences was classified as: 'mild' – no interference with usual daily activities; 'moderate' – some interference with usual daily activities but generally not sufficient to interrupt therapy; and 'severe' – major interference with usual daily activities and generally sufficient to interrupt therapy (not all participants with severe experiences actually discontinued therapy).

Estimation of a substantial rise in nicotine intake during transdermal nicotine therapy was based on the ratio of plasma cotinine concentrations during transdermal nicotine therapy to those at baseline, i.e., prior to quitting smoking (cotinine is the principal, long plasma half-life metabolite of nicotine). A substantial plasma concentration increase was arbitrarily defined as >50% increase from baseline smoking, provided the concentration during transdermal nicotine treatment was above the population mean of 250 μg/L.

For the analysis of concurrent smoking and nicotine intake, smoking was defined as any smoking reported in the 3 days before the follow-up visit for plasma cotinine measurement, or an expired carbon monoxide level of >8 ppm. Heavy consumption of alcohol was defined as consumption of 5 or more standard alcoholic drinks when drinking. In the case of sleep problems, removal of patches before bed was classified as temporary discontinuation of therapy. Family origin was determined by the place of birth of participants' parents.

Data Analysis

Participants were included in the adverse experience counts if 1 or more adverse experiences were reported (tables I and II). The analysis included participants attending 1 or more follow-up visits and individuals providing adverse experience information by telephone only. When a participant reported a particular adverse experience more than once, the most severe (and if the same severity, the earliest) report was counted.

The outcomes studied by Cox regression analyses of predictive factors were application site reactions (excluding musculoskeletal pain) and sleep problems (tables III and IV). For each outcome, unconditional regression models assessed the joint effects of factors selected *a priori* on the occurrence of all adverse experiences, and moderate to severe adverse experiences. Individuals without the adverse experience outcome were used as the reference group. Possible interactions of factors were investigated by adding the appropriate interaction terms. Analyses of the relationships between adverse experiences, concurrent smoking, and plasma concentration data considered all partici-

Table II. Time to onset of common adverse experiences[a]

Adverse experience (no. of affected participants)	Median no. of days to onset[b] (range)	% Participants by dose at the commencement of adverse experiences		
		21mg per 24h	14mg per 24h	7mg per 24h
Any cutaneous application site reaction site (n = 478)	6 (1-85)	79.3	16.9	3.8
erythema (n = 205)	9 (1-85)	71.2	23.4	5.4
rash (n = 72)	12 (1-57)	73.6	22.2	4.2
pruritus (n = 289)	6 (1-85)	76.1	18.3	5.5
irritation (n = 65)	6 (1-68)	81.5	12.3	6.2
vesicles (n = 68)	15 (1-70)	72.1	22.1	5.9
oedema (n = 53)	30 (1-85)	47.2	39.6	13.2
Musculoskeletal ache related to application sites (n = 97)	1 (1-38)	95.9	4.1	0
Sleep problems (n = 669)	1 (1-84)	96.7	3.1	0.1
dreaming (n = 414)	1 (1-84)	96.4	3.1	0.5
other sleep disturbance (n = 447)	1 (1-55)	97.3	2.7	0

a All reports possibly, probably or highly probably related to transdermal nicotine therapy.

b Among affected participants.

© Adis International Limited. All rights reserved.

Table III. Rates and adjusted odds ratios for predictors of application site reactions[a]

Predictor of application site reactions	All reports			Moderate-severe reports		
	adjusted hazard ratio	95% CI	p value	adjusted hazard ratio	95% CI	p value
Skin disorders						
None	1.0			1.0		
Psoriasis or eczema	1.3	1.0 to 1.7	0.049	1.2	0.8 to 1.9	0.350
Other	1.5	1.1 to 2.2	0.025	1.3	0.7 to 2.5	0.471
Age						
≥40y	1.0			1.0		
40y	1.4	1.2 to 1.7	0.001	1.3	0.9 to 1.8	0.118
Gender						
Male	1.0			1.0		
Female	1.2	1.0 to 1.5	0.026	1.3	1.0 to 1.8	0.097
Education level						
Primary/some secondary	1.0			1.0		
Completed trade	1.3	1.0 to 1.8	0.045	1.6	0.9 to 2.6	0.083
Completed secondary	1.0	0.8 to 1.3	0.763	1.2	0.8 to 1.9	0.3
University	1.4	1.1 to 1.8	0.004	1.6	1.1 to 2.3	0.024
Place of birth[b]						
Australasia	1.0			1.0		
Not Australasia	1.3	1.0 to 1.6	0.016	1.8	1.3 to 2.5	<0.001
High nicotine dependence[c]						
No	1.0			1.0		
Yes	1.0	0.8 to 1.2	0.831	0.8	0.6 to 1.1	0.12
Smoking-related disease[d]						
Yes	1.0			1.0		
No	1.2	0.9 to 1.7	0.201	2.0	1.0 to 3.9	0.048

a Unconditional Cox proportional hazards regression analysis on all participants with adverse effects follow up (n = 1392), adjusted for all other factors in the table – the comparison group consists of participants not reporting any application site reaction.

b Non–Australasian-born participants were born in Northern Europe (75%), Southern Europe (9%), Asia (8%) and other locations (8%).

c Modified Fagerström Tolerance Score ≥7 points.[11]

d Cardiovascular disease, malignancy, chronic obstructive pulmonary disease or peptic ulcer.

CI = confidence interval.

pants attending for follow-up 4 to 14 days immediately after commencing transdermal nicotine therapy (tables V and VI).

Statistical tests of paired comparisons included χ^2, Fisher's Exact and Wilcoxon rank sum tests, as appropriate. Data were analysed by the SAS-PC for Windows version 6.12 (SAS Institute, Cary, North Carolina) and EGRET 1.0 (Statistics and Epidemiology Research Corporation, Seattle, Washington) statistical packages. Results are reported as mean ± standard deviation unless otherwise stated.

Results

The mean age of participants was 41 ± 11 years, 56% were female, the mean number of cigarettes smoked per day was 32 ± 12, and the mean Modified Fagerström Tolerance Score[11] was 6.8 ± 1.8. In total, 1260 out of 1392 (90.5%) individuals with follow-up reported 1 or more adverse experiences. Of these, 1090 out of 1392 (78.3%) had 1 or more adverse experiences possibly, probably or highly probably related to transdermal nicotine therapy.

© Adis International Limited. All rights reserved.

Description of Adverse Experiences

The incidence rates of application site reactions, sleep problems and musculoskeletal pain related to application sites are shown in table I. Few experiences were severe, and permanent discontinuation of treatment as a result was rare. Removal of the patch before sleep was commonly practised by individuals experiencing sleep problems (232 out of 669 participants who experienced sleep problems, 34.7%).

Time to onset of adverse experiences varied by type (table II, fig. 1). Sleep problems were most commonly reported to commence from the quit day, whereas application site reactions of pruritus, erythema, rash and irritation typically started later in the first week of therapy. The majority of adverse experiences began during the scheduled period of 21mg per 24-hour transdermal nicotine therapy. Adverse experiences due to application site oedema were relatively delayed (median number of days 30) compared with other types of application site reactions (range of median values 6 to 15 days, p value for difference < 0.001).

Predictors of Application Site Application Site Reactions

At the beginning of the study, 283 out of 1481 participants (19.1%) reported a history of 1 or more pre-existing skin disorders. Eczema was reported by 142 participants (9.6%), psoriasis by 57 participants (3.8%) and other skin problems by 87 participants (5.9%).

Application site reactions of any severity were reported more often by participants who were younger, had a history of skin disorders, were born outside Australasia, or had a university or trade

Table IV. Rates and adjusted odds ratios for predictors of sleep problems[a]

Predictor	All reports			Moderate-severe reports		
	adjusted hazard ratio	95% CI	p value	adjusted hazard ratio	95% CI	p value
Age						
≥40y	1.0			1.0		
40y	1.0	0.8 to 1.1	0.707	0.9	0.7 to 1.2	0.45
Gender						
Male	1.0			1.0		
Female	1.2	1.0 to 1.4	0.012	1.6	1.2 to 2.1	<0.001
Education level						
Primary/some secondary	1.0			1.0		
Completed trade	1.2	0.9 to 1.5	0.203	1.2	0.8 to 1.8	0.320
Completed secondary	1.1	0.9 to 1.4	0.197	1.2	0.9 to 1.7	0.138
University	1.1	0.9 to 1.3	0.639	1.0	0.8 to 1.4	0.837
Quit smoking at wk 4[b]						
No	1.0			1.0		
Yes	1.4	1.2 to 1.6	<0.001	1.5	1.1 to 1.9	0.002
High nicotine dependence[c]						
No	1.0			1.0		
Yes	0.9	0.8 to 1.1	0.198	0.8	0.6 to 1.0	0.046

a Unconditional Cox proportional hazards regression analysis on all participants with adverse effects follow up (n = 1392), adjusted for all other factors in the table – the comparison group consists of participants not reporting any sleep problem.

b Participants reporting not smoking for 28 days and verified by expired carbon monoxide level ≤8 ppm.

c Modified Fagerström Tolerance Score ≥7 points.[11]

CI = confidence interval.

© Adis International Limited. All rights reserved.

Table V. The relationship of concurrent smoking to adverse experiences during the first 4 to 14 days of transdermal nicotine therapy[a]

Adverse experience	Smoked (n = 342) n (%)	Did not smoke (n = 522) n (%)
Any adverse experience	241 (70)	381 (73)
Adverse experience possibly related to transdermal nicotine	204 (60)	334 (64)
Application site reactions	53 (16)	82 (16)
Musculoskeletal ache related to application sites	24 (7)	43 (8)
Any sleep problem	96 (28)[b]	203 (39)[b]
dreaming	58 (17)[c]	120 (23)[c]
other sleep disturbance	58 (17)[b]	137 (26)[b]
Dizziness/lightheadedness	16 (5)	21 (4)
Gastrointestinal problems	46 (13)	84 (16)
Headache	69 (20)[d]	70 (13)[d]
Palpitations/chest pain	5 (1)	6 (1)

a Adverse experiences reported at visit 2, i.e., during the first 4 to 14 days of treatment prior to the follow-up blood sample, by participants correctly using transdermal nicotine. Statistical significance of differences in rates tested by χ^2 or Fishers Exact tests.

b $p < 0.001$.

c $p < 0.05$.

d $p < 0.01$.

school education (table III). These associations were modest (adjusted hazard ratios 0.8 to 1.8). Statistically significant associations with moderate-severe reactions were place of birth outside Australasia, university education and lack of a history of smoking-related disease. A similar majority of participants with (83%) and without (89%) moderate to severe application site reactions were of Northern European or Australasian descent. There was no association of pre-existing skin disorders with moderate-severe application site reactions (hazard ratios ≤1.3, $p > 0.3$).

Predictors of Sleep Problems

Predictors of 1 or both categories of sleep problems (sleep disturbance or dreaming) are shown in table IV. As for predictors of application site reactions, the associations were modest (adjusted hazard ratios ≤1.6). Statistically significant hazard ratios were observed for female gender, smoking cessation at week 4, and high nicotine dependence level (the latter for moderate-severe sleep problems only). In contrast to the multivariate models for application site reactions, there were no apparent associations of sleep problems with age, education, or place of birth.

Concurrent Smoking

Concurrent smoking in the first 4 to 14 days of transdermal nicotine therapy was associated with lower rates of sleep problems (28% *vs* 39%, $p < 0.001$) compared with individuals who did not smoke, but with more frequent reports of headache (20% *vs* 13%, $p < 0.01$) [table V].

Substantially Increased Nicotine Intake

Substantial rises in nicotine intake during therapy (18 out of 321, 5.6%) were uncommon, whether patients smoked concurrently with therapy (11 out of 140, 8%) or not (7 out of 181, 4%) [$p = 0.123$]. These participants reported adverse effects related to transdermal nicotine more frequently than other participants (89% *vs* 63%, $p = 0.04$) [table VI]. Specific categories of local and systemic adverse experiences, except for dizziness/lightheadedness (17% *vs* 3%, $p = 0.03$), were not associated with substantially higher nicotine intake. The 7 participants reporting palpitations or chest pain did not have substantially increased nicotine intake.

© Adis International Limited. All rights reserved.

Table VI. The relationship of substantially increased nicotine intake to adverse experiences during the first 4 to 14 days of transdermal nicotine therapy[a]

Adverse experience	Substantial increase (n = 18) n (%)	No substantial increase (n = 303) n (%)
Any adverse experience	16 (89)	222 (73)
Adverse experience possibly related to transdermal nicotine	16 (89)[b]	192 (63)[b]
Application site reactions	5 (28)	54 (18)
Musculoskeletal ache related to application sites	3 (17)	26 (9)
Any sleep problem	7 (39)	97 (32)
dreaming	3 (17)	59 (19)
other sleep disturbance	4 (22)	65 (21)
Dizziness/lightheadedness	3 (17)[b]	10 (3)[b]
Gastrointestinal problems	1 (6)	27 (9)
Headache	3 (17)	44 (15)
Palpitations/chest pain	0 (0)	4 (1)

a Adverse experiences reported at visit 2, i.e., during the first 4 to 14 days of treatment prior to the follow-up blood sample, by participants correctly using transdermal nicotine. Statistical significance of differences in rates tested by χ^2 or Fisher's Exact tests. Substantial nicotine intake based on plasma cotinine increase of >50%, provided the second plasma concentration was >250 ng/ml.

b $p < 0.05$.

Discussion

The principal findings of this study of 24-hour transdermal nicotine therapy are that: (i) at most there is only a small increased risk of application site reactions in patients with a history of skin disorders; (ii) concurrent smoking is associated with decreased rather than increased problems sleeping; and, (iii) substantially increased plasma nicotine concentrations are uncommon, even when individuals smoke concurrently with treatment. These findings are significant as they suggest that transdermal nicotine therapy can be prescribed safely to patients with common skin disorders. Additionally, it appears that sleep problems are primarily associated with nicotine withdrawal rather than nicotine excess, raising the possibility that higher doses of nicotine may help to alleviate this problem in selected patients.

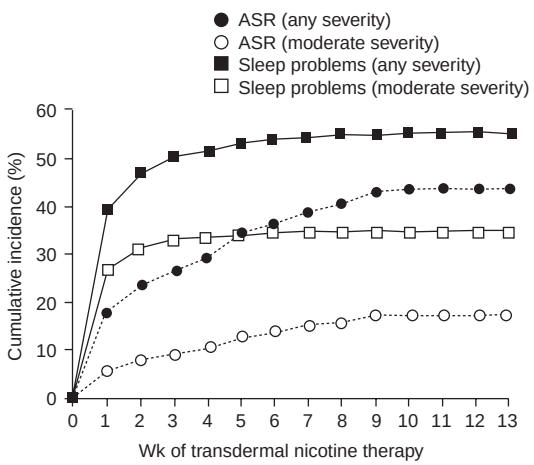

Fig. 1. Cumulative incidence of application site reactions (ASR) and sleep problems during transdermal nicotine therapy.

Details of the timing of onset of application site reactions have not been previously reported in a large study. The relatively late onset of patch site oedema compared with other types of intolerability (30 days *vs* 5 to 15 days) suggests that a different pathophysiological mechanism may be involved (table II). Delayed contact sensitisation to methacrylates in the patch,[12] and to nicotine itself,[13] has been reported and may be the predominant mechanism for application site oedema. On the other hand, application site reactions occurring earlier (pruritus, erythema and musculoskeletal ache) may be attributable to other mechanisms such as the effects of nicotine on local nerve fibres, nicotine-induced dermal vasodilation, occlusion from

© Adis International Limited. All rights reserved.

the patch and direct irritant effects of nicotine and adhesive compounds.[14-15]

Tolerability among participants with a past history of skin disorders is of particular clinical importance (table III). While the rates of application site reactions were somewhat higher in this subgroup of participants (adjusted hazard ratios 1.3 to 1.5), the majority of reactions were mild, and the rates of moderate-severe reactions were increased less (hazard ratios 1.2 to 1.3). It was not possible to determine if the observed increases were artifactual due to increased reporting behaviour associated with having a skin disorder. Given the reassuringly modest increases in reported application site reactions, it seems reasonable to counsel smokers with skin disorders to use the therapy if they are expected to benefit from it.

Other than differences in reporting, there are no established explanations for the other statistically significant associations of application site reactions with younger age, female gender, educational background, place of birth outside Australasia, and lack of smoking-related disease. It is plausible that younger skin is more sensitive to application site irritation than older skin but this has not been previously reported. Individuals born both within and outside Australasia were primarily of European descent, making it unlikely that skin type could explain the higher rate of application site reactions in non–Australasian-born participants.

Consistent with the timing of the onset of the nicotine withdrawal syndrome, sleep problems most commonly commenced from the first day of treatment (table II). The rate of sleep problems was greater than reported by previous studies (48% *vs* 4 to 30%)[1-2,4,6] and a recent meta-analysis (19%).[16] Reports were evenly divided among the subcategories of 'dreaming' and 'other sleep disturbance', similar to the report of Richmond et al.[2] Sleep problems rarely resulted in permanent discontinuation of treatment (table I), consistent with previous reports of 24-hour therapy.[1,8]

As well as their timing, the lower rate of sleep problems in individuals who smoked during transdermal nicotine therapy (tables IV and V) also suggests that sleep problems are primarily due to the nicotine withdrawal syndrome rather than to nocturnal nicotine delivery from replacement therapy. This hypothesis is consistent with the lack of effect of high dose transdermal nicotine replacement therapy on sleep activity in smokers measured by wrist actigraphy.[17] Alternatively, smoking could induce additional tolerance to nicotine, thus masking adverse effects of transdermal nicotine on sleep. Transdermal nicotine has been demonstrated to interfere with sleep architecture in nonsmokers by decreasing rapid eye movement sleep, total sleep time and increasing the time required to fall asleep.[18] However, the effects of nicotine on nonsmokers, who are not tolerant to the effects of nicotine, are not readily generalisable to smokers attempting cessation. Various univariate analyses of controlled clinical trials report substantially lower rates of sleep problems for placebo-treated participants, perhaps misleadingly suggesting that transdermal nicotine itself may affect sleep.[1-2,4] Since transdermal nicotine treatment approximately doubles the rate of smoking cessation,[16,19] and smoking cessation itself is associated with increased sleep disturbance (table IV), multivariate analyses are required to reach this conclusion. Such analyses have not been published to date.

The possibility that transdermal nicotine can adversely affect sleep then raises the issue of whether 16-hour per day therapy has any advantages over 24-hour therapy. Individuals removing the nicotine patch before sleep in a study of 16-hour therapy were not noted to experience higher rates of sleep problems than the placebo control group.[6] However, the generalisability of the adverse experience data from that particular study is in doubt, as the rates of adverse experiences reported were unusually low. Given that nicotine absorption continues from the skin for some hours after patch removal,[20] it is reasonable to expect some sleep disturbance from 16-hour therapy if nicotine is the culprit. Other reports of 16-hour therapy have not discussed this question.[21-24] Given the conflicting data, a randomised comparison of 16-hour and 24-hour therapy, with analytic control for the con-

© Adis International Limited. All rights reserved.

founding effects of smoking cessation, is needed to determine if differential effects on sleep exist, and whether the 2 therapeutic approaches are equally efficacious. One such recent randomised controlled trial comparing 16-hour Nicotrol® and 24-hour Nicoderm® observed similar rates of insomnia in both treatment groups, and a low but somewhat increased rate of abnormal dreams in the 24-hour group (incidence <5%) [S. Shiffman, personal communication].

Our study suggests that substantially increased nicotine intake during standard dose 24-hour replacement therapy is uncommon. Adverse experiences related to treatment were slightly more common in participants with increased intake but no serious symptoms occurred as a result. In particular, no cases of palpitations or chest pain occurred among participants with substantially increased plasma concentrations. However, since only 18 participants experienced increased nicotine intake, this study had very low power to estimate the true rate of uncommon events. Nevertheless, the data are consistent with the findings of recent reviews[16,25] and 2 prospective studies in cardiac disease[26-27] that concluded that there is little or no risk of increased cardiac events during transdermal nicotine treatment.

Conclusion

In conclusion, the pattern of adverse experiences in this cohort study was similar to those reported previously by randomised controlled clinical trials. Sleep problems appeared to be associated with nicotine withdrawal rather than transdermal nicotine treatment, were more frequently reported than application site reactions, and commenced sooner. Both types of adverse experiences rarely caused permanent treatment discontinuation. The associations of predictive factors with adverse experiences were modest, with statistically significant hazard ratios ranging between 1.3 and 2. It is reasonable not to exclude participants with a history of skin disorders from treatment with transdermal nicotine as there appears to be little additional risk of moderate-severe application site reactions. Increased nicotine intake during transdermal nicotine therapy was uncommon, even if participants also smoked, and was associated with a modest increase in the overall rate of adverse experiences related to transdermal nicotine.

Acknowledgements

The work of Dr Gourlay was supported by a National Heart Foundation Overseas Research Fellowship and an Australian National Health and Medical Research Council Public Health Research Fellowship. The AGAIN Study was supported by grants from CIBA-GEIGY (Aust) Ltd., the Anti Cancer Council of Victoria, the Victorian Health Promotion Foundation and the Alfred Hospital. CIBA-GEIGY (Aust) Ltd. provided the transdermal nicotine patches.

With the help of all parties, the study was conducted in accordance with the guidelines for 'Good Clinical Research Practice' issued by the Australian Therapeutic Goods Administration. The study was completed with the help of a dedicated team of research nurses: Lesley Pearson (Deputy Co-ordinator), Christine Woodburn, Janet Wilson, Fiona Williams, Evelyn O'Donnell, Virginia Parker, Sarah Vaughan, Lisa Rowley, Karen McBrearty, Michelle Coleman and Jillian Baird. Secretarial assistance was provided by Nuala Campbell, Lisa Gould and Teresa Koczyk. We are grateful to CIBA-GEIGY (Aust.) who provided the research team with much practical support, particularly in regards to data quality control.

References

1. Imperial Cancer Research Fund 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: 1304-8
2. Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. Med J Aust 1994; 161: 130-5
3. Hurt RD, Dale LC, Fredrickson PA, et al. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up: one year outcome and percentage of nicotine replacement. JAMA 1994; 271: 595-600
4. Gourlay SG, Forbes A, Marriner T, et al. A randomised clinical trial of a second course of transdermal nicotine therapy. BMJ 1995; 311: 363-6
5. Campbell IA, Prescott RJ, Tjeder-Burton SM. Transdermal nicotine plus support in patients attending hospital with smoking-related diseases: a placebo-controlled study. Respir Med 1996; 90: 47-51
6. Sachs DP, Säwe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group therapy. Arch Intern Med 1993; 153: 1881-90
7. Jorenby DE, Smith SS, Fiore MC, et al. Varying nicotine patch dose and type of smoking cessation counseling. JAMA 1995; 274: 1347-52
8. Transdermal nicotine study group. Transdermal nicotine for smoking cessation. JAMA 1991; 266: 3133-8

© Adis International Limited. All rights reserved.

9. Gourlay SG, Forbes A, Marriner T, et al. A prospective study of factors predicting smoking cessation using transdermal nicotine therapy. BMJ 1994; 309: 842-6
10. Gourlay SG, Benowitz NL, Forbes A, et al. Determinants of plasma concentrations of nicotine and cotinine during smoking and transdermal nicotine treatment. Eur J Clin Pharmacol 1997; 51 (5): 407-14
11. Gourlay SG, McNeil JJ. Antismoking products. Med J Aust 1990; 153: 699-707
12. Dwyer CM, Forsyth A. Allergic contact dermatitis from methacrylates in a nicotine transdermal patch. Contact Dermatitis 1994; 30: 309-10
13. Bircher AJ, Howald H, Rufli T. Adverse skin reactions to nicotine in a transdermal therapeutic system. Contact Dermatitis 1991; 25: 230-6
14. Smith EW, Smith KA, Maibach HI, et al. The local side effects of transdermally absorbed nicotine. Skin Pharmacol 1992; 5: 69-76
15. Hogan DJ, Maibach HI. Adverse dermatological reactions to transdermal drug delivery systems. J Am Acad Dermatol 1992; 22: 811-4
16. Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Safety 1998; 18: 297-308
17. Wolter TD, Hauri PJ, Schroeder DR, et al. Effects of 24-hr nicotine replacement on sleep and daytime activity during smoking cessation. Prev Med 1996; 25: 601-10
18. Davila DG, Hurt RD, Offord KP, et al. Acute effects of transdermal nicotine on sleep architecture, snoring, and sleep-disordered breathing in nonsmokers. Am J Respir Crit Care Med 1994; 150: 469-74
19. Silagy C, Mant D, Fowler G, et al. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet 1994; 343: 139-42
20. Benowitz NL, Chan K, Denaro CP, et al. Stable isotope method for studying transdermal drug absorption. Clin Pharm Ther 1991; 50: 286-93
21. Tonnesen P, Norregaard J, Simonsen K, et al. A double-blind trial of a 16-hour transdermal nicotine patch in smoking cessation. N Engl J Med 1991; 325: 311-5
22. Russell MAH, Stapleton JA, Feyerabend C, et al. Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. Br J Med 1993; 306: 1308-12
23. Foulds J, Stapleton J, Hayward M, et al. Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital. Arch Fam Med 1993; 2: 417-23
24. Kornitzer M, Boutsen M, Dramaix M, et al. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. Prev Med 1995; 24: 41-7
25. Benowitz NL, Gourlay SG. The cardiovascular safety of nicotine: implications for nicotine replacement therapy. JACC 1997; 29: 1422-31
26. Working Group for the Study of Transdermal Nicotine in Patients With Coronary Artery Disease. NRT for patients with coronary artery disease. Arch Intern Med 1994; 154: 989-95
27. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med 1996; 335: 1792-8

Correspondence and reprints: Dr *Steven G. Gourlay*, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA.
E-mail: goo@gene.com

© Adis International Limited. All rights reserved.