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A Meta-Analysis to Assess the Incidence of Adverse Effects Associated with the Transdermal Nicotine Patch

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Summary

To estimate the frequency of adverse effects associated with the use of the transdermal nicotine patch, we abstracted and analysed data from 47 reports of 35 clinical trials. The meta-analysis presented here represents a synthesis of data from 41 groups of nicotine patch recipients totalling 5501 patients, and 33 groups of placebo recipients totalling 3752 patients. Smoking abstinence was the primary outcome in 32 of the trials, and relief of colitis symptoms was the primary outcome in 2 of the trials; 1 study of contact sensitisation was included in the skin irritation analysis. The patch was clearly effective as an aid to smoking abstinence. Despite the large number of patients in the analysis, few adverse cardiovascular outcomes (myocardial infarction, stroke, tachycardia, arrhythmia, angina) were reported, and no excess of these outcomes was detected among patients assigned to nicotine-patch use. The incidences of several minor adverse effects were clearly elevated among the nicotine-patch groups, especially sleep disturbances, nausea or vomiting, localised skin irritation and respiratory symptoms, but the background rates and risk ratios varied considerably across studies. The incidence of nausea or vomiting appeared to be lowest when the patch dose was tapered. The results of this meta-analysis indicate that very large studies would be needed to assess the effect of the patch, if any, on serious, rare outcomes. These results also suggest that the rate of minor adverse effects might be lowered by modifying patch-use protocols.

To date, there have been well over 100 published reports of comparative studies of the transdermal nicotine patch. The patch has appeared effective as an aid to smoking cessation in a large majority of reports, including those reports arising from clinical trials.[1-48] Nevertheless, many of these reports have also observed associations between the patch and a number of undesirable adverse effects, such as skin irritation and sleep disturbances. Furthermore, the adverse cardiovascular effects of cigarette use raises the possibility that the patch may also have such effects, which would be of concern if the nicotine patch was used to treat patients with severe cardiac disease.[49,50] In an attempt to assess the incidence of adverse effects associated with nicotine patch use, we conducted a

meta-analysis of randomised placebo-controlled trials.

Methods

Article Abstraction

Articles for this analysis were identified by Ciba Geigy and by our own search of the MEDLINE database. Ciba Geigy sent copies of all articles they had identified to Epidemiology Resources Inc., including reports for 5 unpublished studies of the nicotine patch sponsored by Ciba Geigy. We conducted literature searches based on the terms transdermal, nicotine and human. All the published studies supplied by Ciba Geigy appeared in our MEDLINE search. All articles were reviewed and categorised into the following groups: comparison studies, case reports and case series, other research and reports in humans (primarily trials with only one treatment group, descriptive studies and pharmacokinetic studies), review articles,[51] and all others. The cutoff date for our search was December 1, 1996.

Only studies supplying data on safety outcomes were usable for our purposes. To minimise bias because of self selection for patch use and self reporting of symptoms, we examined only randomised trials. To minimise publication bias (which has been found to be most severe for small studies[52]) and abstraction effort, we required at least 20 patients per treatment arm. We identified 111 published reports of comparison studies. Four of the Ciba Geigy-sponsored unpublished reports were comparison studies, bringing the total reports of comparison studies to 115. These 115 initial reports were distributed as follows:

- at least 20 patients in each treatment arm [78 (68%)]
- adverse effect data presented [83 (72%)]
- randomised [85 (74%)]
- all 3 criteria met [46 (40%)].

Because some studies were published in several reports and others were published in the same report, each study was assigned a unique identification number (study ID). The 46 reports that met our criteria presented results from 34 different randomised trials,[1-46] 2 of which were crossover trials.[32,41] For the skin-irritation analysis, we added a study of contact sensitisation that used nicotine and placebo patches simultaneously on each person.[47] To minimise bias in reports of subjective outcomes, we included only the placebo-patch controls in our analyses; this led us to drop 3 control groups.[11,29,30,46] Two of the included studies employed nicotine gum and placebo gum in addition to patches.[15,16,41] One trial involved only different doses of nicotine patches;[14] this trial was used only in the nicotine-dose regression analyses (described in the statistical methods section). Two of the included studies were of ulcerative colitis rather than smoking cessation; their inclusion had negligible impact on the results, in part because they contributed only 1.6% of the included patients.

Forms were developed to abstract pertinent data from study reports. The abstracted data included basic demographics, study protocol information (exclusion criteria, treatment duration and regimen details), information on compliance, dropout and smoking cessation and adverse events experienced during the treatment period. The forms were reviewed, pilot tested using 8 randomly selected articles and subsequently revised. For consistency, data from the selected studies were abstracted by 1 person; about one-third of the trials were re-abstracted by another abstractor for quality control purposes. The data were then entered into data files to be used for analysis. All entries were checked against paper records.

Most of the patients in most of the studies were middle-aged; no pregnant women took part in any of the studies analysed. In a few studies age ranges rather than mean ages were reported, in which case the mean age was estimated as the midpoint of the range. Except for one study comprising mostly young men [2-4,9] mean ages in the included studies ranged from 37 to 56 years with a median age of 45 years. Over 80% of the studies had between one-third to two-thirds women, so that the overall gender ratio was near to 1. 'Nicotine dose' was com-

puted for each group as the initial daily *assigned* dose from all sources (patch and/or gum). This computation corresponds to an intent-to-treat analysis, as it does not adjust dose for noncompliance, for patient use of cigarettes during treatment, or for other violations of treatment protocols (which were often unreported or not reported in detail).

We abstracted data from 41 groups of nicotine patch recipients (5687 patients in total) and 33 groups of placebo recipients (3752 patients) from the studies. Most of the nicotine patch groups used patches containing nicotine in the range of 17 to 25mg, but 4 (365 patients)[14,29,30,33,36] used patches of ≥28mg, 10 (1793 patients) [5-8,10,15,16,20,21,23-28,32,41] used patches of 14 or 15mg and 2 (167 patients) [6,7,41] used patches of 7 or 8mg. Most of the placebo groups used effectively inert patches, but 9 (1155 patients) [1-4,17,20-22,42-45,47] used 'placebo' patches that contained small doses of nicotine. The dose delivered by the placebo patch was recorded as the placebo dose when it could be determined; 1mg was recorded if the placebo dose was noted as <1mg. Many studies varied the assigned nicotine (active) patch dose according to the bodyweight or smoking habit of patients; for those studies we used our estimate of the average initial dose assigned to the nicotine-patch treatment arm. Only 1 study compared groups with 24 hour and waking-only use of an active patch;[7,8] of the remainder, most involved 24 hour use, although 8 (with 10 active and 9 placebo groups) [10,15,16,23-28,32,40,41] involved waking-only use. No study involved comparisons of groups with or without counselling, although 18 studies (with 21 active and 18 placebo groups) supplied counselling to all patients. 16 studies (with 18 active-patch groups) provided for tapering of the patch dose as the study progressed; the exact tapering protocol varied somewhat across studies. For the 2 studies[15,16,41] (3 groups) that provided nicotine gum, we added an extra 10mg nicotine (equivalent to 5 pieces of Nicorette™) to the estimated daily dose for the treatment arms using active gum; their inclusion had negligible impact on the results, in part because they contributed only 3.1% of the nicotine-patch patients and only 0.7% of the placebo-patch patients.

Studies differed as to whether they classified certain minor outcomes as adverse events or smoking withdrawal symptoms and this discrepancy in turn affected our counts of these outcomes. All the studies that collected data on withdrawal symptoms did so by having patients use a subjective rating scale of symptom severity. The studies sometimes reported an average severity score for the withdrawal symptoms, but none of them reported these data in terms of the number of patients experiencing the symptoms. For that reason, we could not incorporate withdrawal symptom data into our analyses. For example, 3 studies[18,19,35,39] classified nausea as a withdrawal symptom rather than an adverse event and the number of patients experiencing nausea was unknown in all 3 studies. Other outcomes affected by this problem are tachycardia, chest tightness, constipation and other gastrointestinal effects, headache, sleep disturbance, tremor, cough, alterations in taste, dizziness, mouth sores, sore throat and heartburn (some of these were not separate categories in our analysis, but would have been added to a broader category of outcome such as gastrointestinal effects).

Of the 34 randomised trials, 28 studies excluded patients on the basis of cardiovascular conditions or risk factors (e.g. recent myocardial infarction or stroke, ischaemic heart disease, certain types of cardiac arrhythmia); these exclusions probably reduced the frequency of cardiovascular outcomes and thus limited our power to detect patch effects on such outcomes. Four studies [20,21,43-45] specified certain cardiovascular conditions or risk factors as inclusion criteria, with the objective of investigating patch safety as well as smoking cessation rates in patients at risk; however, patients with certain other types of cardiovascular disease were excluded from these studies as well.

We wish to emphasise that smoking abstinence data abstracted for our analysis were for the treatment period in each study. They do not include information regarding abstinence beyond the treatment period, which was not available for many of

the abstracted studies. The data are therefore not ideal for measuring effectiveness, but are nonetheless included here for interested readers.

Statistical Methods

Data abstraction and analysis were conducted by separate personnel, but no blinding was imposed. Data were initially tabulated in 3-way cross-classifications of treatment by outcome by study. Three primary analysis approaches were applied to these tables. First, a p-value for the association of treatment with the outcome risk within studies was computed using the Mantel-Haenszel method,[53] with 'study ID' as the stratifying variable. If the total number of outcome events was ≤10, an exact mid-p value[53,54] was computed instead. Second, the Mantel-Haenszel summary risk ratio (*not* odds ratio) estimate and 95% confidence limits were computed;[53,55,56] if the outcome was uncommon (≤10 events), the exact median-unbiased odds-ratio estimate and mid-p confidence limits were computed instead.[53,55] Third, study-specific risk ratios were computed for all studies reporting at least 1 outcome in at least 2 treatment arms. Parallel analyses were also done using Mantel-Haenszel odds-ratio and rate-ratio analyses.[48,50] These yielded essentially identical results and so are not reported here.

For adverse effects recorded in at least 5 patients across trials we performed several more analyses. First, we performed a test for nonrandom heterogeneity (variation) of the risk ratio across studies.[53,56] We then conducted regression analyses of the relation of treatments to outcome risks using log-linear (exponential) models for the risks that allowed the baseline (placebo) risks to vary across studies[57] and that allowed for observation error in those risks.[58] The treatment (nicotine-patch) coefficient was also treated as random[59] if the homogeneity p-value was less than 0.05 (above this cutoff, type of model did not make an important difference). This type of model allows the risk ratios to vary across studies and provides a summary risk ratio whose confidence interval reflects both random error and variation across studies. These models also enabled us to treat as continuous variables both nicotine dose and duration of use and to express results as the estimated risk ratio comparing a 21 mg/day nicotine dosage to no nicotine.

For those outcomes for which the homogeneity p-value was less than 0.05, we modified the random-coefficient regression models to estimate the impact on nicotine-patch effects of dose tapering (reduction in assigned dose during the course of treatment), duration of treatment, timing of use (24 hours versus waking hours only), use of nicotine gum, counselling and the age and gender distributions of the studies. These variables were chosen because they were recorded in all or nearly all of the studies and so sufficient numbers of patients were available for most of these analyses.

Results

Table I summarises the crude data abstracted from the included trials. The table includes crude percentages of patients experiencing the various events recorded in order to provide the reader with a rough idea of the average frequency of the events. We caution, however, that the frequencies for some outcomes varied considerably across studies (especially for compliance, smoking abstinence, nausea or vomiting and skin irritation) and that the crude percentages are inflated by the exclusion of studies not reporting events.

The studies were equally divided between those reporting much better compliance among nicotine-patch groups and those reporting no difference, with the former tending to be studies with nicotine-dose tapering. All studies reported more smoking abstinence among the nicotine-patch treated patients than the placebo-patch treated patients, but the degree of this benefit varied dramatically, from slight to 4-fold improvement in abstinence rates. Results for nausea or vomiting showed extreme variation, but this could in part be attributed to the small numbers of events among the placebo groups in most of the studies. Studies showing little or no increase in nausea or vomiting among the nicotine-patch groups all involved tapering. The effect of the nicotine patch on skin irritation was also highly

Table I. Summary of data by outcome for studies reporting the outcome

Outcome (no. of studies[a])	Patients assigned nicotine patch		Patients assigned other treatment	
	no. events/ no. patients	crude %	no. events/ no. patients	crude %
Withdrew from study				
Resumed smoking (5)	31/323	10	45/326	14
Adverse effect intolerance (19)	127/3216	4	55/2164	3
Noncompliance (9)	46/788	6	58/794	7
Reasons not related to study (4)	6/247	2	14/247	6
Lost to follow-up (4)	80/574	14	98/576	17
Other reasons (3)	18/106	17	21/108	19
Unspecified reasons (14)	716/2175	33	853/2185	39
Compliance (10)	667/1785	37	412/1378	30
Smoking abstinence (26)	1298/4508	29	509/3400	15
Cardiovascular outcomes				
Myocardial infarction (2)	3/36	1	3/362	1
Stroke (2)	1/354	0.3	2/357	1
Tachycardia (1)	2/239	1	0/238	0
Palpitations (4)	2/446	0.4	8/451	2
Angina (1)	1/239	0.4	1/238	0.4
Arrhythmia (3)	11/406	3	9/411	2
Hypertension (2)	8/354	2	5/357	1
Other body system outcomes				
Gastrointestinal symptoms				
Nausea, vomiting (11)	141/2,67	5	99/2238	4
Constipation, diarrhea, dyspepsia (6)	60/1336	4	54/1282	4
Unimproved ulcerative colitis (2)	32/75	43	45/77	58
Musculoskeletal symptoms (4)	21/513	4	11/421	3
Respiratory symptoms				
Asthma (1)	0/115	0	2/119	2
Bronchitis (1)	9/115	8	5/119	4
Other respiratory symptoms (3)	23/892	3	2/497	0.4
Urogenital symptoms (1)	0/115	0	1/119	1
Neurological symptoms (2)	4/115	3	1/159	1
Localised skin irritation (23)	884/3584	25	410/3102	13
General systemic outcomes				
Chest pain (5)	11/1228	1	7/1200	1
Headache (11)	264/2624	10	206/2133	10
Fatigue, malaise (5)	8/414	2	9/358	3
Sweating (2)	51/164	31	46/164	28
Dizziness (9)	117/1599	7	87/1104	8
Sleep disturbance (7)	280/1490	19	117/1451	8
Alteration in taste (4)	27/1101	2	16/1043	2
Alteration in mood, mental status (4)	85/382	22	61/380	16
Urticarial reaction (1)	0/115	0	1/119	1
Unspecified adverse effects (8)	106/822	13	64/598	11

a Number of trials in which the outcome was reported in at least 1 patient.

variable, but in all but one study the risk was at least 10% higher among the nicotine-patch groups compared with the placebo-patch groups. In the study that applied nicotine and placebo patches to the same patients simultaneously,[47] the skin irritation risk was over 70% higher at the nicotine-patch sites than the placebo-patch sites.

Table II presents the basic statistical results for those outcomes that occurred in both nicotine and placebo-patch groups (risk ratios are zero or undefined if no outcomes occurred in the nicotine or placebo group; thus tachycardia and urticarial reaction are excluded from the table). The Mantel-Haenszel risk ratios are estimates of the effect of any nicotine-patch use versus placebo-patch use, whereas the regression risk ratios are estimates of the effect of a 21mg increase in the nicotine dose of a patch (e.g. a 21mg patch versus a completely inert placebo). The Mantel-Haenszel and regression results are quite similar for most outcomes; the exceptions involve outcomes for which the study-specific estimates are highly variable.

Few studies reported any occurrences of myocardial infarction, stroke, tachycardia, angina, or arrhythmia, perhaps in part because of study exclusions. No excess risks of these outcomes are apparent, although the estimates are extremely imprecise. The patch did appear to increase the risk of hypertension and chest pain, although these apparent effects were within the range expected of random associations. There are, however, several noteworthy differences between the nicotine-patch and placebo-patch treatment arms. Perhaps most importantly, nicotine-patch groups recorded higher rates of study withdrawal because of intolerance to adverse effects. Among patients who did not withdraw from the study, reported compliance with the assigned treatment was on average higher in the nicotine-patch treatment arms, as was reported smoking abstinence. However, it should be noted that 'compliance' refers to compliance among persons remaining in the study and so excludes those who withdrew.

The risks of minor, but common, problems were also higher among the nicotine-patch treated patients, including sleep disturbances, localised skin irritation, mood alterations and respiratory symptoms. The apparently large effect of treatment with the nicotine patch on 'other respiratory symptoms' is probably in part because of the presence of only 2 such outcomes among the placebo groups. The patch also appeared to increase the risk of taste alterations, bronchitis and neurological symptoms, but again these apparent effects were within the range expected of random associations.

The homogeneity p-values in the last column indicate that there is considerable nonrandom variation in risk ratios for withdrawal because of unspecified reasons, compliance, nausea or vomiting and skin irritation; hence, for these outcomes, table II gives the range of study-specific risk ratios rather than summary risk ratios. The heterogeneity of risk ratios on unspecified withdrawal is probably only an artifact of the varying definition of this outcome across studies and we do not consider it further here. For all the common outcomes, the variation in baseline risks appears to be a major source of heterogeneity.

Table III presents results of regressions that include the product of nicotine use with one of either dose tapering, duration of treatment, timing of patch (24 hours versus waking hours only) or counselling. Each 'change in risk ratio' in the table is an estimate of the amount that the patch effect (risk ratio) would change if the treatment protocol were changed with respect to each variable. For example, the estimate of 1.60 for tapering under the 'compliance' subheading means that the patch risk ratio was estimated to be 60% higher (on average) when tapering was provided than when it was not. Table III corroborates the impression that the improved compliance seen in the nicotine-patch groups tends to be more pronounced when dose tapering is provided. There also appears to be a tendency toward a stronger effect on compliance when duration is longer (i.e. the nicotine patch improves compliance more when treatment is longer) and a suggestion that 24-hour use of the patch diminishes the effect. In contrast, the effects of the patch on smoking abstinence and skin irritation do

Table II. Estimated risk ratios (RR) and 95% confidence limits (CL) for studies reporting the outcome

Outcome (no. of studies[a])	M-H or mid-p RR[b] (95% CL)	RR per 21mg nicotine[c] (95% CL)	Homogeneity p-value
Withdrew from study			
Resumed smoking (5)	0.69 (0.46-1.04)	0.61 (0.38-0.99)	0.46
Adverse effect intolerance (19)	1.79 (1.31-2.44)	2.12 (1.49-3.02)	0.20
Noncompliance (9)	0.80 (0.55-1.15)	0.73 (0.48-1.11)	0.24
Reasons not related to study (4)	0.43 (0.17-1.08)	0.32 (0.13-0.82)	0.20
Lost to follow-up (4)	0.82 (0.63-1.06)	0.79 (0.59-1.07)	0.86
Other reasons (3)	0.87 (0.52-1.45)	0.71 (0.25-2.01)	0.55
Unspecified reasons (14)	Range of RR: 0 to 1.07		0.0011
Compliance (10)	Range of RR: 0.99 to 4.11		0.0001
Smoking abstinence (26)	1.93 (1.76-2.11)	1.76 (1.62-1.90)	0.62
Cardiovascular outcomes			
Myocardial infarction (2)	1.00 (0.17-5.83)		0.27
Stroke (2)	0.54 (0.02-6.73)		0.38
Palpitations (4)	0.26 (0.04-1.10)		0.54
Angina (1)	1.00 (0.025-39)		
Arrhythmia (3)	1.26 (0.56-2.87)	1.43 (0.48-4.24)	0.24
Hypertension (2)	1.60 (0.52-5.48)	1.79 (0.50-6.45)	0.20
Other body system outcomes			
Gastrointestinal symptoms			
Nausea, vomiting (11)	Range of RR: 0.38 to 7.00		0.0012
Constipation, diarrhea, dyspepsia (6)	1.08 (0.75-1.55)	1.18 (0.87-1.59)	0.25
Unimproved ulcerative colitis (2)	0.73 (0.54-1.01)	0.59 (0.38-0.91)	0.68
Musculoskeletal symptoms (4)	1.48 (0.71-3.07)	1.27 (0.91-1.77)	0.55
Respiratory symptoms			
Bronchitis (1)	1.91 (0.63-6.54)	2.12 (0.62-7.27)	
Other respiratory symptoms(3)	5.68 (1.64-38.7)	5.96 (1.79-19.9)	0.55
Neurological symptoms (2)	3.80 (0.51-10.6)		0.57
Localised skin irritation (23)	Range of RR: 1.10 to 5.57		0.011
General systemic outcomes			
Chest pain (5)	1.52 (0.60-3.85)	2.02 (0.69-5.94)	0.50
Headache (11)	1.06 (0.89-1.25)	1.02 (0.87-1.19)	0.46
Fatigue, malaise (5)	0.63 (0.25-1.61)	0.93 (0.26-3.33)	0.16
Sweating (2)	1.11 (0.81-1.52)	1.23 (0.80-1.90)	0.095
Dizziness (9)	1.00 (0.78-1.28)	1.04 (0.72-1.48)	0.38
Sleep disturbance (7)	2.31 (1.89-2.83)	2.03 (1.71-2.41)	0.22
Alteration in taste (4)	1.55 (0.82-2.93)	1.24 (0.65-2.37)	0.15
Alteration in mood mental status (4)	1.39 (1.08-1.78)	1.55 (1.10-2.19)	0.081
Unspecified adverse effects (8)	1.24 (0.95-1.63)	1.29 (0.92-1.79)	0.63

a Number of trials in which the outcome was reported in at least 1 individual.

b Mantel-Haenszel (M-H) for active versus placebo patch if at least 5 outcomes in each of nicotine patch and other groups across all studies, mid-p estimate otherwise.

c Maximum-pseudolikelihood estimate from log-linear regression;[57]– denotes fewer than 5 cases on active and placebo patch; if homogeneity $p < 0.05$, range of study-specific estimates given instead.

Table III. Estimates of the effects of duration, tapering, timing, and counselling on the risk ratios for the effect of nicotine patch versus placebo (from Log-Linear Random Effects Risk Regressions)

	Change in risk ratio (95% confidence limits)	Homogeneity p-value[a]
Compliance		0.009
Tapering (*vs* none)	1.60 (1.35-1.84)	
Duration (4 *vs* 2 months)	1.24 (1.12-1.37)	
24-hour use (*vs* waking hours only)	0.82 (0.69-0.98)	
Counselling (*vs* none)	0.98 (0.82-1.16)	
Smoking abstinence		0.31
Tapering (*vs* none)	0.98 (0.83-1.16)	
Duration (4 *vs* 2 months)	0.98 (0.83-1.16)	
24-hour use (*vs* waking hours only)	0.85 (0.68-1.06)	
Counselling (*vs* none)	0.99 (0.82-1.19)	
Nausea or vomiting		<0.0001
Tapering (*vs* none)	0.27 (0.13-0.56)	
Duration (4 *vs* 2 months)	1.50 (0.94-2.40)	
24-hour use (*vs* waking hours only)	1.11 (0.67-1.83)	
Counselling (*vs* none)	0.88 (0.53-1.48)	
Localised skin irritation		0.02
Tapering (*vs* none)	1.08 (0.90-1.30)	
Duration (4 *vs* 2 months)	1.04 (0.88-1.23)	
24-hour use (*vs* waking hours only)	0.96 (0.76-1.22)	
Counselling (*vs* none)	1.29 (1.05-1.58)	

a p-Value for hypothesis that there is no variation in patch effect beyond that accounted for by tapering, duration, timing, counselling and baseline risk (from deviance test for overdispensation[60])

not appear to be much affected by tapering, duration, or 24-hour use (although there is a hint that the effect on abstinence may be weakened by 24-hour use).

The most striking finding is the reduced association of nicotine with nausea or vomiting in studies that involved tapering. The 4-fold reduction in the risk ratio estimate suggests that tapering may help prevent nausea or vomiting because of the patch. Although the regression results also suggest that nausea or vomiting is more of a problem with longer duration of use, the use of tapering may more than compensate for duration effects. Patch effects on nausea or vomiting did not appear to be much changed by 24-hour use, but because of the wide confidence intervals the regression results are not very informative in this regard. The homogeneity p-value in the final column of table III shows that the three factors considered in the table, along with variations in background risk, cannot fully explain the variation among study results seen for compliance, nausea or vomiting, or skin irritation. We also regressed the nicotine-patch risk ratios on mean age and the proportion of women in each trial, but no relation of these variables to patch effects were apparent and these results are not presented. The lack of age effect may be caused by the fact that most of the patients in the trials included here were concentrated in middle age.

Because nausea or vomiting could quickly interfere with compliance, we present the study-specific results in table IV. The highest risk ratio is from a study of ulcerative colitis, which is not surprising given that most of these patients were nonsmokers and hence would be nicotine sensitive (although the dose used was much lower than with the other trials). When this study was deleted, the homogeneity p-value remained small ($p = 0.01$). Several studies exhibited risk ratios of around one or less and all these studies involved tapering. This obser-

vation explains the highly significant association of tapering with lower risk ratios (table III). Nonetheless, of the remaining studies, the 2 exhibiting the largest risk ratios also used tapering. Thus, the association of tapering with effect reduction is markedly inconsistent and the variation in risk ratios among the studies in table IV remains largely unexplained.

Discussion

We wish to emphasise that the absence of apparent heterogeneity for many of the outcomes may be due only to imprecision of the results. Also, the lack of impact of counselling on compliance and abstinence seen in table III may only be because of the heterogeneous nature of the counselling, compliance and abstinence variables across the studies. For example, some studies used group counselling, others individual counselling; some used behavioural, other used supportive; and durations varied. Unfortunately, there were too few studies within each type of counselling to allow informative comparisons of different types of counselling.

The present data also leave open other important questions. It appears that the acute effects of the nicotine patch on serious outcomes (such as myocardial infarction and stroke) cannot be determined reliably from the randomised placebo-controlled trials performed to date, because the risk of these outcomes was simply too low in the studies to have yielded enough events for an informative analysis; this is so despite the fact that the trials involved over 9000 participants and is no doubt in part because of the cardiovascular exclusions used in most of the trials. Our analysis also could not address the effect of nicotine patch use in adolescents. Many studies specifically excluded persons <18 years old. The remainder did not report whether adolescents were included; if any participated in the studies, however, their number must have been low given the high mean ages reported.

After our search was completed, Joseph et al.[48] presented results from a double-blinded randomised placebo-controlled trial of 584 cardiovascular outpatients. Their results are consistent with those reported here, in so far as they did not detect an elevation of adverse outcomes in the active treatment group, but their confidence intervals were compatible with a broad range of possible effects. Such findings suggest that a very large observational (postmarketing) study will be required to assess any effect of the patch on serious cardio-

Table IV. Study-specific results for studies reporting nausea or vomiting

% of patients with symptoms		Total no. of patients		Treatment duration (days)	Dose[a]	Hours worn per day	Risk ratio (95% confidence limits)	Reference
active treatment arms	placebo treatment arms	active treatment arms	placebo treatment arms					
19	25	124	124	84	15(t)	Waking	0.77 (0.48-1.24)	11
5.0	2.5	120	120	56	22	24	2.00 (0.51-7.81)	13
2.3	3.2	842	844	84	21(t)	24	0.71 (0.40-1.26)	14
5.8	1.3	156	157	70	21(t)	24	4.53 (0.99-20.6)	23
4.3	3.0	800	400	126	15 (t)	Waking	1.42 (0.74-2.71)	24, 25
3.5	9.3	113	107	126	15 (t)	Waking	0.38 (0.12-1.17)	26
4.1	0.7	145	144	112	15 (t)	Waking	5.96 (0.73-49)	27-29
35	5.0	40	40	182	8	Waking	7.00 (1.70-28.8)	41[b]
5.6	4.9	179	143	84	21(t)	24	1.14 (0.45-2.92)	43
11	3.4	115	119	84	21	24	3.36 (1.13-10.0)	44

a Estimated average daily dose in active treatment arms.

b Study of ulcerative colitis.

Abbreviation: t = tapered.

vascular outcomes. Such a study will face formidable obstacles to valid design and interpretation. It will be especially difficult to find an appropriate comparison group for nicotine patch users and to adjust for the self-selection that distinguishes patch users from those who attempt to stop cigarette smoking using other methods or those who continue to smoke. In addition, the risk of any rare serious adverse effects must be weighed against the effects of continuing to smoke (which may often be the only alternative to patch use).

As apparent from the tables, the effects of the patch on some of the more minor outcomes (such as nausea or vomiting) can be highly variable. The data we have collected did not identify all the sources of this variation. We wish to emphasise that the primary purpose of most of the trials was to estimate the effect of the nicotine patch on smoking cessation, not to characterise adverse effects. Study protocols varied widely in the methods used to collect, analyse and report adverse effect data. This methodological variation may be a major source of the observed variation in patch effects.

Publication bias is often raised as a major issue in meta-analysis.[52] In the present situation, we cannot imagine how trials observing many serious adverse effects would go selectively unreported, but we have no data bearing on this issue.

To avoid confounding problems, we chose to limit our analyses to questions for which there were within-study comparison data. Only one study[7,8] included in our analysis compared waking *vs* 24-hours use (and this study had only 55 waking-use and 51 24-hour patients) and no study included counselling or brand name comparisons. We thus could not meaningfully address main effects of waking *vs* 24-hour use, counselling, or patch brand. Lack of detail in reported data also prohibited analysis of the effects of smoking concomitant with patch use.

Despite the limitations of our analysis, some important patterns can be discerned in the results. The 32 smoking-cessation studies used in our analyses illustrate the efficacy of the nicotine patch (over placebo) for short term smoking abstinence. They also suggest that dose tapering will aid in encouraging compliance with recommended use and may aid in avoiding nausea or vomiting, although the results are inconsistent in the latter regard. It appears that 24-hour use is no better than waking-hour use in achieving such objectives. The data also confirm that certain minor adverse effects, such as sleep disturbances and skin irritation, are common but are limited to a minority of users. It is noteworthy that the excess skin irritation observed here is likely to be a nicotine effect, since the controls wore placebo patches. Although the data are from randomised trials, these results are tentative in that the correlation of treatment factors resulted in imprecise estimates of the effects of these factors. For example, dose tapering is used only when duration of use exceeds 4 weeks and so it is difficult to disentangle the effect of tapering from that of duration; also, we cannot be sure that tapering preceded the reduced frequency of adverse effects in trials with tapering.

We note again that the above conclusions did not change in any meaningful way when the few treatment arms involving nicotine gum or ulcerative colitis patients were excluded, in part because these arms contributed only a limited proportion of patients to each analysis and in part because patch effects did not significantly differ between these and the other studies.

The heterogeneity we observed suggests that minor adverse effects might be minimised by as yet untested protocols, such as intermittent wearing, or use of patch sizes other than those currently available. Randomised trials could be used to compare current protocols and patches with new protocols and patches designed to minimise adverse effects while maintaining smoking abstinence. Because the trials included here suggest that adverse effects may be an important cause of patch discontinuance, we wish to encourage further trials to help determine better patch-use protocols.

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