American Journal of Epidemiology

Vol. 145, No. 4
Printed in U.S.A.

Nicotine Patches in Smoking Cessation: A Randomized Trial among Over-the-Counter Customers in Denmark

Jette Sønderskov,[1] Jørn Olsen,[1,2] Svend Sabroe,[1] Lucette Meillier,[1] and Kim Overvad[1]

The authors examined the effect of 24-hour nicotine patches in smoking cessation among over-the-counter customers in Denmark, based on a randomized double-blind placebo-controlled trial. Participants were consecutive customers to whom nicotine patches were offered as the only treatment. Forty-two pharmacies in the areas of Aarhus and Copenhagen in Denmark participated in the trial, and 522 customers who smoked 10 or more cigarettes per day were randomized to either nicotine patches or placebo from January to March 1994. Customers with chronic diseases and pregnant or breastfeeding women were excluded from the trial. Twenty-four-hour patches were offered free of charge during a 3-month period. Those smoking 20 or more cigarettes per day started on a dose of 21-mg/day patches. Customers who smoked less started on patches of 14 mg/day; and for all of the participants, the dose was gradually reduced to 7-mg/day patches during the study period. Smoking behavior and compliance were recorded by means of self-administered questionnaires and telephone interviews. Smoking status was recorded in intervals of 4 weeks, which was fixed to be a treatment period, and 26 weeks after inclusion. There was a significant increase in smoking cessation rates after 8 weeks of follow-up but only among smokers who started on 21-mg/day patches. There was a marked placebo effect at each time of contact during the trial, especially in those smoking fewer than 20 cigarettes per day. Although the noncompliance rate was high overall due to discontinuation in the use of patches by relapsed smokers, noncompliance among successful quitters was low. More side effects were seen in the nicotine group than in the placebo group, but none of the reported side effects were serious. It appears that regular healthy smokers who were customers of nonprescribed nicotine patches and who received 21-mg/day nicotine patches benefited from the active treatment (44.1% stopped smoking after 4 weeks), but almost as many stopped smoking in the placebo group (37.3% after 4 weeks). No significant differences in smoking cessation rates were seen among smokers who started with the low-dose nicotine or placebo patches. *Am J Epidemiol* 1997;145:309–18.

drug administration routes; drugs, non-prescription; nicotine; placebo effect; randomized controlled trials; smoking cessation

Cigarette smoking is the single most important preventable cause of cancer and premature death (1), and 20 percent of all deaths in developed countries are presently attributed to tobacco smoking (2). Consequently, smoking cessation has a high priority in preventive health; and several strategies have been applied, such as public information campaigns on health consequences of smoking and suggestions concerning change in smoking behavior, high taxation on cigarettes, restriction on tobacco advertising and promotional activities, enforced prohibition on sale of tobacco products to underaged youth, tobacco-free schools and workplaces, and tobacco education programs in schools. Several types of individual interventions have been implemented, e.g., self-help manuals and advice/therapy or group programs in smoking cessation clinics or at workplaces headed by physicians or psychologists; and these interventions have had varying success (3–9). From the 1920s to the 1940s, several investigators assumed that nicotine was responsible for the compulsive use of tobacco among smokers (10), and additional data supported this theory (10). From the 1950s, the health consequences of smoking were documented (11–16); however, a pharmacologic aid in smoking cessation, nicotine gum, was not launched until 1973 (17). Since then, other nicotine replacement methods (10, 18–22) have been developed to relieve nicotine withdrawal symptoms, such as nicotine gum, patches, and nasal sprays.

During the late 1980s and the early 1990s, the efficacy of nicotine replacement therapy compared

Received for publication June 16, 1995, and accepted for publication October 2, 1996.
[1] Department of Epidemiology and Social Medicine, University of Aarhus, Aarhus, Denmark.
[2] Danish Epidemiology Science Centre, Aarhus, Denmark.
Reprint requests to Dr. Jørn Olsen, Department of Epidemiology and Social Medicine, University of Aarhus, Nørrebrogade 44, Building 2C, DK-8000 Aarhus C, Denmark.

with placebo treatment has been examined in a number of trials. Meta-analyses evaluating the potency of nicotine gum showed a decrease in efficacy over time when used in low-intervention smoking cessation programs, such as programs implemented in a general practice setting (23, 24). Efficacy was greater when combined with intensive programs in specialized smoking cessation clinics (24, 25).

Nicotine gum does have unpleasant side effects (20), and so as an alternative delivery system, the nicotine patch was developed in 1984. Absorption of nicotine from the patches is transdermal, and contrary to the nicotine gum, the plasma level of nicotine is constant during the period of use. Better compliance is expected because it is easier to use (18–20).

The effect of nicotine patches has been evaluated in randomized placebo-controlled trials in volunteers recruited by public advertisements or by invitation. In general, the method appears to work independently of the trial settings (26–28), even with little counseling (28, 29).

Until recently, nicotine patches were sold only by prescription in most countries. However, over-the-counter sale has been permitted in Denmark since December 1991. Studies estimating the value of nicotine patches in an over-the-counter situation are needed, especially since use without counseling or support could be applied on a large scale.

The first objective of the present study was to estimate short-term smoking cessation rates among consecutively selected customers of nicotine patches at a number of pharmacies in Denmark. The intention was to evaluate smoking cessation by means of nicotine patches as close to a real-life situation of over-the-counter use as possible. No additional smoking cessation methods or use of biomarkers to determine smoking status were applied.

The second objective of the study was to evaluate smoking cessation on a long-term basis.

MATERIALS AND METHODS

The study was a randomized double-blind placebo-controlled trial aimed at obtaining two groups, each with approximately 250 customers. The trial was carried out in collaboration with the Department of Epidemiology and Social Medicine, University of Aarhus, Denmark, and Ciba-Geigy, Inc., Denmark. The Department of Epidemiology and Social Medicine was responsible for collecting, analyzing, and reporting the data; and Ciba-Geigy monitored the study at the pharmacies.

Setting and study participants

Recruitment of customers took place at 42 pharmacies in the areas of Aarhus and Copenhagen (equivalent to about 20 percent of all pharmacies in Denmark) from January to March 1994. No public announcement of the trial was made; and to minimize talk about the study among people, it was decided to spread the first day of inclusion for the participating pharmacies over a 3-week period. Furthermore, only a few participants were included from sparsely populated areas. All 18-year-old or older customers at the pharmacy who had decided to buy 24-hour nicotine patches and who smoked at least 10 cigarettes per day (inclusion criteria) were asked to join the study, and they were offered the patches free of charge. Information about potential participants was obtained by self-reported medical history. Pregnant or breastfeeding women and customers with cardiovascular disease, endocrine disease, diabetes, peptic ulcer, or reduced kidney or liver function were excluded from the trial (exclusion criteria).

Potential candidates were asked to give oral and written consent and to refrain from using any other nicotine products during the trial, in accordance with trial conditions set forth by the Danish National Board of Health. Among the 573 registered customers who fulfilled the inclusion criteria, 522 gave informed consent and were randomized by means of randomized sequential treatment packages. Details of the study population and the outcome of randomization are described in table 1.

For practical reasons, four employees from Ciba-Geigy, Inc., provided instructions concerning the trial procedure for the staff at the participating pharmacies and distributed trial patches to the participating pharmacies. A Ciba-Geigy employee was in contact with the participating pharmacies at least once a week. Selected pharmacists at each participating pharmacy were responsible for recruiting and dispensing the patches to trial members.

Treatment

Twenty-four-hour nicotine patches (Nicotinell) were provided for a 12-week period equivalent to three treatment periods. Customers who smoked 20 cigarettes or more per day were randomized to use one 21-mg/day patch per day during the first 4 weeks equivalent to one treatment period (active patches release 21 mg of nicotine in 24 hours), 14-mg/day patches (14 mg of nicotine/24 hours) during the second 4-week treatment period, and 7-mg/day patches (7 mg of nicotine/24 hours) during the final 4 weeks. Smokers of fewer than 20 cigarettes per day used 14-mg/day patches during the first two treatment pe-

TABLE 1. Baseline characteristics of trial members according to dose of treatment among pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Variables	14-mg/day patches						21-mg/day patches					
	Nicotine			Placebo			Nicotine			Placebo		
	No.	%	Mean (SD*)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Sex												
M	30	41.7		42	58.3		61	50.8		59	49.2	
F	89	51.7		83	48.3		75	47.5		83	52.5	
Age (years)												
17–34	55	46.2		64	53.8		50	49.5		51	50.5	
35–44	27	56.3		21	43.7		42	50.0		42	50.0	
≥45	37	48.1	38.2 (12.9)	40	51.9	38.9 (13.7)	44	47.3	39.1 (10.6)	49	52.7	39.9 (10.9)
Education (years)												
≤9	36	50.7		35	49.3		41	42.3		56	57.7	
10	48	50.0		48	50.0		57	53.7		49	46.3	
≥11	35	46.1		41	53.9		37	50.0		37	50.0	
Daily cigarette consumption												
10–14	51	49.0		53	51.0		2	100				
15–19	62	49.2		64	50.8		9	42.9		12	57.1	
20–24	3	37.5		5	62.5		88	48.9		92	51.1	
≥25							37	49.3		38	50.7	
No. of smoking years			20.2 (11.1)			19.5 (12.1)			22.2 (9.8)			22.7 (10.6)
FTQ* score			6.1 (1.9)			6.1 (1.7)			7.0 (1.7)			8.1 (1.6)

* SD, standard deviation; FTQ, Fagerström's Tolerance Questionnaire score (range 0–11) (30).

riods (8 weeks), and 7-mg/day patches during the final treatment period. To ensure that the nicotine and placebo patches were identical in terms of color and odor, the placebo patches contained a pharmacologically negligible amount of nicotine.

Randomization was selected within the two smoking levels. Instructions for proper use of patches were given orally and in writing at the pharmacies. Participants were asked to change the application site of the patch every day, and patches were handed out in 4-week packages equivalent to one treatment period in this study.

Three patch sizes constituted the dose treatment of Nicotinell patches available in public sale in Denmark at that time. The routine treatment procedure was recommended by the pharmaceutical firm and subsequently tested and used in the trial.

Data

Each customer completed a questionnaire at the pharmacy on the day of randomization. Subsequent questionnaires were mailed from the Department of Epidemiology and Social Medicine to the participants in weeks 3 and 7 of the 12-week treatment period and returned in closed envelopes to the pharmacies in weeks 4 and 8, when participants collected patches for the next treatment period. The questionnaires were immediately mailed to the Department of Epidemiology and Social Medicine. Telephone interviews were conducted by two trained interviewers in weeks 12 and 26 or whenever participants dropped out of the trial or reported any side effects.

Data on sociodemographic characteristics, number of previous quit attempts, smoking history, and nicotine dependency (estimated by Fagerström's Tolerance Questionnaire) (30) were collected at the time of randomization. Information was collected at each point of contact throughout the trial period on smoking status during the trial, smoking while using the patches, other kinds of intervention, side effects, and continuous and interrupted use of patches.

Records were kept when dropouts either were absent at the expected time of collecting patches at the pharmacies or reported discontinued use of patches in the questionnaire. It was documented when a participant dropped out because of relapse, discontinued use of the patches, or reported side effects or a lack of perceived effect of the treatment. At the time of the dropout, current smoking status was recorded, and nonsmokers were contacted in week 26 to collect information on smoking behavior.

Successful smoking cessation was defined in the protocol as 1) no reported smoking during a 4-week treatment period; or 2) one episode of slip, which was defined as less than 6 days of smoking within a 4-week period (31). After each 4-week period of follow-up, the point prevalence of smoking was measured.

Relapse was defined as 7 consecutive days of smoking one or more cigarettes (31). Compliance was used to indicate the extent to which the recommended treatment procedure was followed.

Analyses

The results were analyzed according to the "intention to treat" principle and by means of the χ^2 test and the Mantel-Haenszel trend test (16). Bivariate, survival, and logistic regression analyses were conducted in SPSS/PC+ advanced statistics 4.0. The level of statistical significance was set at 0.05 and all confidence intervals as 95 percent. The blinding procedure was not broken until all main results were tabulated. Participants lost to follow-up ($n = 19$) were classified as smokers.

RESULTS

The main results of the study are presented in table 2. In the nicotine patch group, more smokers stopped smoking than in the placebo group; however, the difference was statistically significant only among participants who started on 21-mg/day patches and only after 8 weeks of follow-up. In combined analyses, the point prevalence of nonsmokers decreased from 50 percent after 4 weeks to 17 percent after 26 weeks in the nicotine group; the corresponding values in the placebo group were 44 percent and 11 percent, respectively.

When similar analyses were made using total abstinence to classify nonsmokers, the prevalence of nonsmokers in the combined group decreased for the nicotine treated from 22 percent after 4 weeks to 8 percent after 26 weeks, compared with 17 percent and 5 percent in the placebo group. The relative smoking cessation prevalence proportions were 1.27 (95 percent confidence interval 0.89–1.81) after 4 weeks and 1.83 (0.92–3.65) after 26 weeks.

In table 3 can be seen a statistically significant and moderately better treatment effect among participants treated with 14-mg/day nicotine patches who had 11 or more previous quit attempts. No effect of nicotine treatment can also be seen in relation to duration of previous smoking, daily cigarette consumption, and a high nicotine dependency score ("FTQ score") regardless of starting dose. Furthermore, no differences in smoking cessation rates among men and women according to starting dose and treatment were found. In a combined analysis of the treatment groups, a mod-

TABLE 2. Smoking cessation according to treatment and starting dose of specific patches among pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Smoking cessation after (weeks)	14-mg/day patches						21-mg/day patches					
	Prevalence of nonsmokers				PPR†,‡	95% CI†	Prevalence of nonsmokers				PPR§	95% CI
	Nicotine (n = 119)		Placebo (n = 125)				Nicotine (n = 132)		Placebo (n = 142)			
	No.	%	No.	%			No.	%	No.	%		
4	64	53.8	63	50.4	1.06	0.84–1.34	60	44.1	53	37.3	1.18	0.89–1.57
8	45	37.8	41	32.8	1.15	0.82–1.62	39	28.7	26	18.3	1.56*	1.01–2.40
12	27	22.7	28	22.4	1.01	0.64–1.61	25	18.4	10	7.0	2.61*	1.30–5.23
26	27	22.7	23	18.4	1.23	0.75–2.03	15	11.0	6	4.2	2.61*	1.04–6.53

* $p < 0.05$.
† PPR, prevalence proportion ratio; CI, confidence interval.
‡ Test for trend (14 mg/day): $p = 0.96$.
§ Test for trend (21mg/day): $p = 0.07$.

erately better treatment effect among women was observed, albeit not statistically significant.

As shown in table 4, poor compliance in both groups (less than half used the patches as scheduled in the protocol) was mainly due to the fact that relapsed smokers stopped using the patches. Noncompliance among the remaining nonsmoking trial members was much smaller throughout the treatment period, 11.4 and 12.0 percent in the nicotine and placebo groups, respectively. Compliance results according to initial treatment dose do not differ from the combined result in table 4.

During each 4-week treatment period, skin reactions and minor central nervous system reactions (sleep disturbance, headache, dizziness) were more frequent in the nicotine group (table 5). Skin reactions increased with time, but none of the side effects were serious or led to hospitalization. Side effects were, however, one of the main reasons reported for dropping out in the nicotine group (apart from no perceived effect of treatment and relapse); this was not seen in the placebo group (table 6).

DISCUSSION

Most smoking cessation trials using transdermal patches have been implemented in clinical and general practice settings among volunteers recruited through local advertisements; most of these trials have shown better effects from nicotine than placebo patches (18, 32–41). In general, the difference in abstinence rates between the nicotine and the placebo-treated groups at the end of the treatment period is more pronounced in clinical trials than in general practice trials due to a stronger placebo effect in trials carried out in general practice (18, 28, 32–41). The previously published results indicate that nicotine patches are effective in smoking cessation in clinical settings. These studies do not provide information on the effectiveness of patches when used in public health. One survey with a 6-month follow-up period and self-reported data conducted among a large "real-world" population of elderly, low-income transdermal nicotine users who filled prescriptions through the Pennsylvania Pharmaceutical Assistance Plan tried to describe the pattern of use and outcome of transdermal nicotine therapy in relation to other types of intervention. The results indicated that a comprehensive support system and proper patient instruction in patch use were needed to obtain a higher rate of quitters in the population (42).

The present study was designed to evaluate the efficacy of nicotine patches in an over-the-counter environment without additional support. For that reason, no biomarkers or diaries were used to estimate

TABLE 3. Smoking cessation according to treatment and starting dose stratified by selected variables among pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Smoking cessation after 4 weeks stratified by	14-mg/day patches						21-mg/day patches					
	Nicotine		Placebo		PPR†	95% CI†	Nicotine		Placebo		PPR	95% CI
	All	Nonsmokers (%)	All	Nonsmokers (%)			All	Nonsmokers (%)	All	Nonsmokers (%)		
Sex												
M	30	20 (66.7)	41	26 (63.4)	1.05	0.67–1.34	59	29 (49.2)	58	27 (46.6)	1.06	0.65–1.39
F	86	44 (51.2)	80	37 (46.3)	1.11	0.66–1.24	72	31 (43.1)	79	26 (32.9)	1.31	0.87–1.96
History of regular smoking (years)												
1–29	89	53 (59.5)	94	46 (48.9)	1.22	0.93–1.59	101	52 (51.5)	102	41 (40.2)	1.28	0.93–1.72
≥30	26	11 (42.3)	23	15 (65.2)	0.65	0.38–1.11	30	8 (26.7)	34	12 (35.3)	0.76	0.63–2.80
No. of previous attempts to stop smoking												
1–4	70	43 (61.4)	79	39 (49.4)	1.24	0.93–1.67	87	39 (44.8)	83	35 (42.2)	1.06	0.67–1.33
5–10	22	12 (54.5)	18	8 (44.4)	1.23	0.43–1.55	15	10 (66.7)	20	10 (50.9)	1.13	0.43–1.32
≥11	24	9 (37.5)	24	16 (66.7)	0.56	0.31–1.00*	29	11 (37.9)	34	8 (23.5)	1.62	0.75–3.45
Daily cigarette consumption												
10–14	51	36 (70.6)	51	39 (76.5)	1.24	0.92–1.67						
15–19	65	28 (43.1)	70	34 (48.6)	0.89	0.61–1.28						
20–24							97	44 (45.4)	102	39 (38.2)	1.19	0.85–1.65
≥25							34	16 (47.1)	35	14 (40.0)	1.18	0.69–1.34
FTQ† score												
1–6	69	45 (65.2)	74	42 (56.8)	1.15	0.67–1.88	24	12 (50.0)	23	9 (31.1)	1.28	0.41–1.50
7–8	33	15 (45.5)	36	15 (41.7)	1.09	0.54–1.57	54	26 (48.1)	52	20 (38.5)	1.25	0.81–1.96
9–11	14	4 (28.6)	10	5 (50.0)	0.57	0.20–1.61	52	22 (42.3)	62	24 (38.7)	1.09	0.59–1.43

* $p < 0.05$.
† PPR, prevalence proportion ratio; CI, confidence interval; FTQ, Fagerström's Tolerance Questionnaire score.

TABLE 4. Compliance according to treatment among pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Compliance after (weeks)	Nicotine patch		Placebo patch		PPR*	95% CI*
	All	Compliance (%)	All	Compliance (%)		
4	255	115 (45.1)	267	107 (40.1)	1.13	0.92–1.37
8	156	52 (33.3)	154	61 (39.6)	0.84	0.62–1.13
12	96	36 (37.5)	97	45 (46.4)	0.80	0.57–1.12

* PPR, prevalence proportion ratio; CI, confidence interval.

TABLE 5. Side effects according to treatment of pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Type of side effects†	Nicotine patch		Placebo patch		PPR§	95% CI§
	No.‡	Stated side effects (%)	No.‡	Stated side effects (%)		
Reaction after 4 weeks	255		267			
Skin		75 (29.4)		49 (18.4)	1.60	1.17–2.20*
Gastrointestinal		7 (2.7)		9 (3.4)	0.81	0.31–2.15
Central nervous system		19 (7.5)		7 (2.6)	2.84	1.22–6.65*
Cardiac		1 (0.4)		4 (1.5)	0.26	0.03–2.33
Reaction after 8 weeks	156		154			
Skin		61 (39.1)		34 (22.1)	1.77	1.24–2.53*
Gastrointestinal		1 (0.6)		5 (3.2)	0.20	0.02–1.67
Central nervous system		4 (2.6)		2 (1.3)	1.97	0.37–10.62
Cardiac		1 (0.6)		2 (1.3)	0.44	0.05–5.39
Reaction after 12 weeks	96		97			
Skin		42 (43.8)		31 (32.0)	1.37	0.93–1.97
Gastrointestinal		4 (4.2)		4 (4.1)	1.01	0.26–3.92
Central nervous system		11 (11.5)		1 (1.0)	11.1	1.46–84.39*
Cardiac		2 (2.1)		1 (1.0)	2.02	0.19–21.92

* $p < 0.05$.

† Reactions are categorized as follows: skin—itching, erythema, skin eruption, allergic reaction; gastrointestinal—nausea, vomiting, diarrhea, constipation, flatulence, abdominal pain, dry mouth, abnormalities of salivation and taste; central nervous system—sleep disturbance, headache, dizziness; cardiac—palpitation, chest pain.

‡ Number of trial members at the beginning of the period.

§ PPR, prevalence proportion ratio; CI, confidence interval.

smoking status, and no psychological or behavioral support was added to the pharmacologic treatment.

Our results concerning smoking cessation among smokers treated with nicotine patches were similar to those in previous papers (18, 28, 32–35, 38–41), but the placebo effect in the present study was stronger than in most other studies (28, 32, 37), especially for those who smoked fewer than 20 cigarettes per day at inclusion. Smokers participating in our study were probably highly motivated since trial members were potential customers who had decided to invest in an expensive treatment (in Denmark, a 1-month supply of Nicotinell patches costs $120), which perhaps could explain the high placebo effect. In contrast to other trials in this field, there were no advertisements for potential trial candidates, and the fact that the patches were provided free of charge was not announced in advance to avoid less motivated customers in the trial.

The lack of effect, especially in the group that started on the low-dose treatment, might be due to insufficient nicotine supply to meet their nicotine need. The distribution of the Fagerström's Tolerance Questionnaire score (30) showed substantial overlap between those who started on the 21- and the 14-mg/day doses. Of those who started on the 14-mg/day dose, 40 percent had a Fagerström's Tolerance Questionnaire score (30) of more than 6 (figure 1), perhaps due to an unintended underreporting of smoking at the beginning of the trial or to a recently reduced daily cigarette consumption. Nicotine dependency estimated by the Fagerström Tolerance Questionnaire may perhaps be a better way of allocating smokers to the proper treatment level than asking for the daily number of cigarettes at the time of trial inclusion.

An effect of the nicotine patch was observed among participants treated with 21-mg/day nicotine patches who had a Fagerström's Tolerance Questionnaire score between 7 and 11 points, whereas no effect of the nicotine patches was observed among participants treated with 14 mg/day and a similar Fagerström's

TABLE 6. Reasons for leaving the smoking cessation study according to treatment of pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Reason	Nicotine patch		Placebo patch		PPR†	95% CI†
	No. leaving the study	%	No. leaving the study	%		
0–4 weeks						
Started to smoke	24	25.3	30	27.3	0.90	0.48–1.69
No perceived need for treatment	6	6.3	7	6.4	0.99	0.85–1.16
Side effect	19	20.0	5	4.5	5.25	2.03–13.57*
No perceived effect of treatment	29	30.5	51	46.4	0.51	0.29–0.90
Other reason	10	10.5	11	10.0	1.06	0.43–2.62
No stated reason	7	7.4	6	5.4	1.38	0.45–4.25
All	95	100.0	110	100.0		
5–8 weeks						
Started to smoke	18	28.6	20	33.3	0.80	0.37–1.73
No perceived need for treatment	7	11.1	3	5.0	2.38	0.60–9.38
Side effect	16	25.4	8	13.3	2.21	0.88–5.59
No perceived effect of treatment	17	27.0	22	36.7	0.64	0.30–1.37
Other reason	4	6.3	6	10.0	0.72	0.19–2.69
No stated reason	1	1.6	1	1.7	0.95	0.36–2.52
All	63	100.0	60	100.0		
9–12 weeks						
Started to smoke	37	55.2	52	70.3	0.60	0.30–1.22
No perceived need for treatment	10	14.9	10	13.5	1.21	0.47–3.13
Side effect	10	14.9	6	8.1	2.08	0.72–6.01
No perceived effect of treatment	4	6.0	2	2.7	2.44	0.45–13.21
Other reason	4	6.0	3	4.0	1.61	0.35–7.41
No stated reason	2	3.0	1	1.4	2.40	0.23–25.41
All	67	100.0	74	100.0		

* $p < 0.05$.
† PPR, prevalence proportion ratio; CI, confidence interval.

Tolerance Questionnaire score. The randomization apparently produced two comparable groups, and only 19 randomized customers were lost to follow-up. Logistic regression controlling for gender, age, Fagerström's Tolerance Questionnaire score, pharmacy effect, age when started smoking, starting dose,

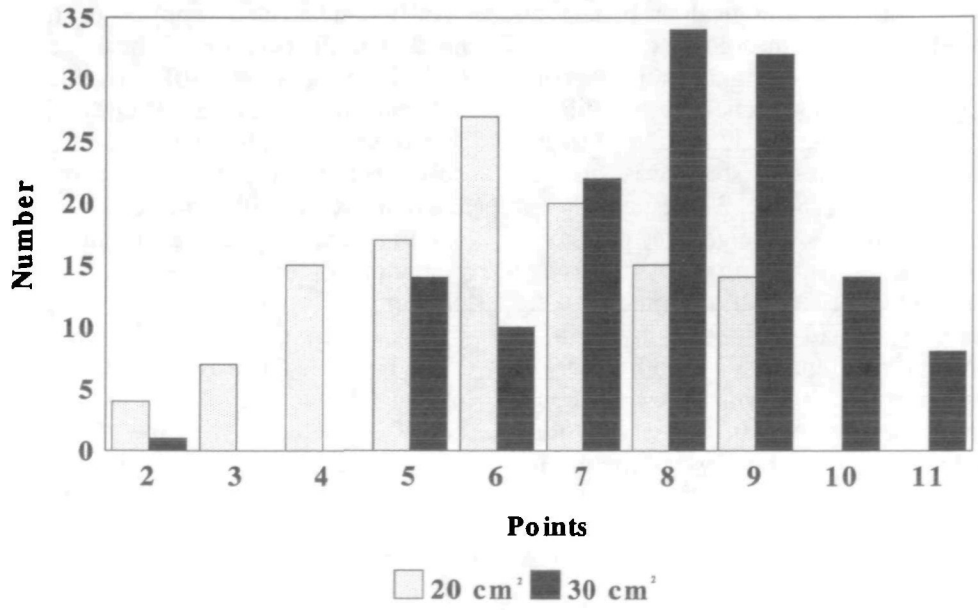

FIGURE 1. Fagerström's score for the Nicotinell group, Aarhus and Copenhagen, Denmark, January to March 1994.

school and vocational education was done but did not change the point estimate toward a significant result inasmuch as the analysis showed an odds ratio of 1.32 (95 percent confidence interval 0.82–1.64).

All attempts were made to blind the treatment during the trial and in the analyses. However, of the placebo-treated participants, more than expected according to the null hypothesis guessed the type of treatment at the end of the treatment period (table 7). The effect of such a blinding failure would probably be a reduction of the placebo effect.

The low compliance in our study was expected since no one encouraged the relapsed smokers to continue use of the patches. On the contrary, they were warned against getting too much nicotine, and they had to promise at entry not to use additional nicotine products while using the patches.

Our data on smoking are probably reliable since smoking status was recorded in self-administered questionnaires, by telephone interviews conducted by "neutral" interviewers, and without any social pressure to provide specific answers. Furthermore, the use of biomarkers would not eliminate the impact of nondifferential misclassification since these methods have a rather low sensitivity (43, 44). Furthermore, smoking is socially more acceptable in Denmark than in most other countries, and different studies of smoking behavior among Danes have shown reliable self-reported smoking data (45–47).

This trial suggests that transdermal nicotine treatment in an over-the-counter situation should probably be allocated according to a nicotine dependency score. The trial also indicates that the success rate of over-the-counter use of patches was better than expected, especially among the placebo-treated; however, the difference in outcome between the two treatment groups was smaller than in most other trials with nicotine patches. Transdermal nicotine treatment appears to be relatively safe when used in a population without any contraindication, and the current study indicates that it is possible to administer this treatment in a pharmacy setting.

TABLE 7. Evaluation* of the blinding procedure in a smoking cessation study of pharmacy customers who made over-the-counter purchases in Aarhus and Copenhagen, Denmark, January to March 1994

Guess†	Actual use			
	Nicotine patch		Placebo patch	
	No.	%	No.	%
Nicotine patch	75	30.6	47	18.3
Placebo patch	97	39.6	139	54.1
Do not know	73	29.8	71	27.6

* $p = 0.001$; df = 2.

† Self-reported guessing of which treatment study participants received according to actual treatment.

ACKNOWLEDGMENTS

This study was partly funded by Ciba-Geigy, which also supplied the nicotine and placebo patches.

The authors thank Gitte Bjørnø and Annemette Christensen, who conducted the interviews; Annemette Christensen, who coordinated data collection and prepared the manuscript; and Marianne Godt Hansen, who was responsible for language revision of the manuscript.

The study was approved by the Regional Ethics Committee in the County of Aarhus and by the National Board of Health, and it met the standards set by the Declaration of Helsinki and the Good Clinical Practice Guidelines.

REFERENCES

1. Doll R, Peto R, Wheatley K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994;309:901–11.
2. Peto R, Lopez AD, Boreham J, et al. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 1994;339:1268–78.
3. Popham WJ, Potter LD, Bal DG, et al. Do anti-smoking media campaigns help smokers quit? Public Health Rep 1993;108: 510–13.
4. Strategies to control tobacco use in the United States: a blueprint for public health action in the 1990's. Washington, DC: Department of Health and Human Services, 1991. (NIH publication no. 92–3316; Smoking and Tobacco Control monograph 1).
5. Elders MJ, Perry CL, Eriksen MP, et al. The report of the surgeon general: preventing tobacco use among young people. Am J Public Health 1994;84:543–7.
6. Glynn TJ, Greenwald P, Mills SM, et al. Youth tobacco use in the United States—problem, progress, goals, and potential solutions. Prev Med 1993;22:568–75.
7. Townsend J, Roderick P, Cooper J. Cigarette smoking by socioeconomic group, sex, and age: effects of price, income, and health publicity. BMJ 1994;309:923–7.
8. Cummings KM, Sciandra R, Markello S. Impact of a newspaper mediated quit smoking program. Am J Public Health 1987;77:1452–3.
9. Orleans CT, Slade J. Nicotine addiction: principles and management. New York, NY: Oxford University Press, 1993.
10. The health consequences of smoking: a report of the surgeon general. Rockville, MD: Public Health Service, 1988:1–639.
11. Doll R, Hill AB. Smoking and carcinoma of the lung. Br Med J 1950;221:740–8.
12. Doll R, Hill AB. A study of the aetiologi of carcinoma of the lung. Br Med J 1952;225:1271–86.
13. Doll R, Hill AB. The mortality of doctors in relation to their smoking behavior. Br Med J 1954;228:1451–5.
14. Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking. Br Med J 1956;233:1071–81.
15. Doll R, Hill AB. Mortality in relation to smoking: 10 years' observations of British doctors. Br Med J 1964;248: 1399–410.
16. Doll R, Hill AB. Mortality in relation to smoking: 20 years' observation on male British doctors. Br Med J 1976;273: 1525–36.
17. Fernö O, Lichtneckert SJA, Lundgren EG. A substitute for tobacco smoking. Psychopharmacology 1973;31:201–4.

18. Mulligan SC, Masterson JG, Devane JG, et al. Clinical and pharmacokinetic properties of transdermal nicotine patch. Clin Pharmacol Ther 1990;47:331–7.
19. Rose JE, Jarvik ME, Rose KD. Transdermal administration of nicotine. Drug Alcohol Depend 1984;13:209–13.
20. Rose JE, Herskovic JE, Trilling Y, et al. Transdermal nicotine reduces cigarette craving and nicotine preference. Clin Pharmacol Ther 1985;38:450–6.
21. Sutherland G, Russel MAH, Stapleton J, et al. Nasal nicotine spray: a rapid nicotine delivery system. Psychopharmacology 1992;108:512–18.
22. Sutherland G, Stapleton JA, Russell MAH, et al. Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet 1992;340:324–9.
23. Hughes JR, Gust SW, Keenan RM, et al. Nicotine vs placebo gum in general medical practice. JAMA 1989;261:1300–5.
24. Cepeda-Benito A. Meta-analytical review of the efficacy of nicotine chewing gum in smoking treatment programs. J Consult Clin Psychol 1993;61:822–30.
25. Lam W, Sze PC, Sacks HS, et al. Meta-analysis of randomised controlled trials of nicotine chewing-gum. Lancet 1987;2: 27–30.
26. Silagy C, Mant D, Fowler G, et al. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet 1994;343:139–42.
27. Tang JL, Law M, Wald N. How effective is nicotine replacement therapy in helping people to stop smoking? BMJ 1994; 308:21–6.
28. Fiore MC, Smith SS, Jorenby DE, et al. The effectiveness of the nicotine patch for smoking cessation. JAMA 1994;271: 1940–7.
29. Campbell IA. Nicotine patches in general practice. BMJ 1993; 306:1284–5.
30. Fagerström KO, Schneider G. Measuring nicotine dependence: a review of the Fagerström tolerance questionnaire. J Behav Med 1989;12:159–82.
31. Ossip-Klein DJ, Bigelow G, Parker RS, et al. Classification and assessment of smoking behavior. Health Psychol 1986; 5(suppl):3–11.
32. Abelin T, Buehler A, Müller P, et al. Controlled trial of transdermal nicotine patch in tobacco withdrawal. Lancet 1989;1:7–10.
33. Hurt RD, Lauger GG, Offord KP, et al. Nicotine-replacement therapy with use of a transdermal nicotine patch—a randomized double-blind placebo-controlled trial. Mayo Clin Proc 1990;65:1529–37.
34. Tønnesen P, Nørregaard J, Simonsen K, et al. A double-blind trial of 16-hour transdermal nicotine patch in smoking cessation. N Engl J Med 1991;325:311–15.
35. Study G. Transdermal nicotine for smoking cessation. JAMA 1991;266:3133–8.
36. Yudkin P, Mant D, Jones L, et al. Effectiveness of a nicotine patch in helping people to stop smoking: results of a randomised trial in general practice. BMJ 1993;306:1304–8.
37. Russell MAH, Stapleton JA, Feyerabend C, et al. Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. BMJ 1993;306:1308–12.
38. Rose JE, Levin ED, Behm FM, et al. Transdermal nicotine facilitates smoking cessation. Clin Pharmacol Ther 1990;47: 323–30.
39. Daughton DM, Heatley SA, Prendergast JJ. Effect of transdermal nicotine delivery as an adjunct to low-intervention smoking cessation therapy. Arch Intern Med 1991;151: 749–52.
40. Westman EC, Levin ED, Rose JE. The nicotine patch in smoking cessation. Arch Intern Med 1993;153:1917–23.
41. 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.
42. Orleans CT, Resch N, Noll E, et al. Use of transdermal nicotine in a state-level prescription plan for the elderly: a first look at "real-world" patch users. JAMA 1994;271:601–7.
43. Patrick DL, Cheadle A, Thompson DC, et al. The validity of self-reported smoking: a review and meta-analysis. Am J Public Health 1994;84:1086–93.
44. Hughes JR, Krahn D. Blindness and the validity of the double-blind procedure. J Clin Psychopharmacol 1985;5:138–43.
45. Hansen H, Rasmussen NK, Poulsen J. Life style and health habits in Denmark: research report. Copenhagen: Minister of Health, 1994:1–72.
46. Nielsen PE, Krarup NB, Astrup J, et al. Change in smoking habits among the Danes, 1958–1976. Ugeskr Laeger 1978; 140:2528–32.
47. Nielsen PE, Krarup NB. Tobacco consumption in Denmark, 1920–1975. Ugeskr Laeger 1976;138:2511–16.