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Original Contributions

Predicting Smoking Cessation

Who Will Quit With and Without the Nicotine Patch

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Objective.—To identify predictors of smoking cessation success or failure with and without transdermal nicotine patch treatment.

Design.—Two independent randomized, double-blind, placebo-controlled studies using the nicotine patch assessing outcome at the end of treatment and at 6-month follow-up; each study used a different mode of adjuvant counseling.

Patients.—Subjects were daily smokers (≥15 cigarettes per day), aged 21 to 65 years with expired air carbon monoxide levels of at least 10 ppm, and motivated to quit. Eighty-eight subjects participated in study 1, and 112 subjects participated in study 2.

Intervention.—Study 1 consisted of 8 weeks of 22-mg nicotine patch therapy with intensive group counseling. Study 2 consisted of 4 weeks of 22-mg nicotine patch therapy and 2 weeks of 11-mg nicotine patch therapy with brief individual counseling.

Main Outcome Measures.—The prediction of smoking cessation (at end of treatment and after 6 months) based on pretreatment and intratreatment measures in smokers using active or placebo nicotine patches.

Results.—Pretreatment markers, such as the Fagerstrom Tolerance Questionnaire score, number of cigarettes smoked per day, years smoked, expired air carbon monoxide level, or baseline blood nicotine and cotinine levels, showed no consistent relationship with successful smoking cessation across both studies. Of the intratreatment markers examined, withdrawal severity and nicotine replacement levels also were not consistently predictive of cessation success. However, any smoking during the second week of treatment was a consistent and powerful predictor of failure at the end of treatment and after 6 months. Among active nicotine patch patients who smoked at all during week 2 after quitting, 83% and 97% (studies 1 and 2, respectively) were smoking at 6-month follow-up. Conversely, abstinence during the second week of treatment predicted successful smoking cessation. Among active nicotine patch patients who were totally abstinent during week 2 after quitting, 46% and 41% (studies 1 and 2, respectively) were abstinent at 6-month follow-up. Of all nicotine patch patients in both studies who were smoking at 6-month follow-up, 74% began smoking during week 1 or 2. Among all placebo patch patients who were smoking at 6-month follow-up, 86% began smoking during week 1 or 2.

Conclusions.—Smoking status (abstinent or smoking) during the first 2 weeks of nicotine patch therapy, particularly week 2, was highly correlated with clinical outcome and can serve as a powerful predictor of smoking cessation. Early smoking behavior also predicted outcome among placebo patch users. Traditional measures of dependence are not consistently predictive of cessation success. Clinicians are advised to emphasize the importance of total abstinence after a quit attempt and to follow-up with patients within the first 2 weeks of quitting; smoking during this critical time should be assessed and treatment may be altered as appropriate.

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NUMEROUS clinical trials have shown that the transdermal nicotine patch system helps people quit smoking.[1] Quit rates, however, vary widely across these trials. This may be due in part to the marked heterogeneity of smokers in the United States today. If one could identify those smokers likely to succeed or fail with or without nicotine patch treatment, it would be possible to make treatment decisions on a more rational basis and increase each patient's odds of quitting successfully.

For example, smokers judged to be at risk for failure might be given a more potent adjuvant treatment, such as intensive group counseling, to boost treatment effectiveness.[2] Other smokers might be switched to a wholly different treatment, such as nicotine fading or aversive smoking.[3]

Despite much research, accurate and consistent predictors of successful smoking cessation have not been identified. Variables that have proven predictive in some studies do not predict in others, and when predictive relations are found, they are modest. For example, gender has been found to predict treatment success in some studies[4,5] but not in another.[6] Similarly, measures that are hypothesized to reflect nicotine dependence (eg, number of cigarettes smoked per day, blood nicotine levels, and expired air carbon monoxide [CO_a] levels) have predicted treatment success weakly and inconsistently.[7,8] One reported measure of nicotine dependence, the Fagerstrom Tolerance Questionnaire[9] has predicted long-term success in some studies[8,10] but has not been consistently related to outcome among nicotine patch users.[11,12] The inconsistency in predictive relations suggests that the accuracy and sensitivity of any given predictor is affected by factors that vary from study to study, such as the target population and type of cessation treatment.

We examined predictors of treatment success and failure among smokers with and without the nicotine patch. The research included two studies with two independent samples of smokers. Moreover, two different adjuvants were used

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with nicotine patch therapy and placebo patch therapy: (1) intensive group counseling and (2) brief individual counseling. Independent samples and different types of adjuvants provided the opportunity to assess the generalizability of our findings.

To identify predictors of successful cessation with and without the nicotine patch, we assessed a number of variables that could be quickly and easily measured by a clinician and therefore would have broad clinical utility. We evaluated measures collected prior to quitting (pretreatment variables) and early in the quitting attempt (intratreatment variables).

METHODS

Two studies using nicotine patch therapy and two different modes of adjuvant therapy were conducted sequentially. In study 1, patch therapy was paired with state-of-the-art intensive group counseling; in study 2, patch therapy was paired with brief individual counseling that could be conducted in a clinician's office. The methods used in both studies and efficacy results are described in more detail elsewhere.[2]

Subjects

Subjects were recruited through media announcements in Madison, Wis, a city of 190 700 residents. Inclusion criteria consisted of age 21 to 65 years, a history of smoking at least 15 cigarettes per day during the past year, expired CO_a level of at least 10 ppm (as determined at screening), and motivation to quit smoking. Exclusion criteria included presence of cardiovascular disease, pregnancy or lactation, regular use of psychotropic drugs, current symptomatic psychiatric disorder, alcohol or other drug abuse, chronic dermatologic disorders, and/or use of any experimental medication within the past 30 days. Eighty-eight subjects participated in study 1, and 112 subjects participated in study 2.

Study Designs

After enrollment, the subjects and the clinician agreed on a quit date. Subjects were told to stop smoking on this date at which time nicotine patch and adjuvant counseling treatments commenced. On the quit date and once per week during the treatment period the following data were gathered at the clinic site: self-reported smoking status for the previous week (confirmed by expired CO_a assay), vital signs, and questionnaire and study drug information. Between visits, subjects kept a smoking diary each day that contained an eight-item withdrawal survey.[13] Serum samples for nicotine and cotinine were collected at a screening visit before the quit date and at 4 weeks following the quit date. Both studies were double blinded and placebo controlled.

Study 1 consisted of 8 weeks of 22-mg nicotine patch therapy (or equivalent placebo patch), and study 2 consisted of 6 weeks of nicotine patch therapy—4 weeks of 22-mg patch therapy followed by 2 weeks of 11-mg patch therapy (or placebo). In both studies, counseling sessions occurred for 8 weeks, and subjects were contacted at 6 months following their quit dates to determine their smoking status. Self-report was confirmed by expired CO_a assay.

Six-month follow-up data were used to assess predictors of success and failure because the nicotine patch was licensed by the Food and Drug Administration at this end point of study 1, and we wanted to prevent confounding of results due to the extraordinarily high rates of off-study prescription patch use immediately after licensing.

Transdermal Nicotine

The transdermal nicotine delivery system (PRO*STEP*, Lederle Laboratories, Wayne, NJ) used in these studies was a hydrogel matrix reservoir containing nicotine. The patch was applied once a day, worn for 24 hours, and delivered a total absorbed dose of either 22 mg or 11 mg of nicotine. Placebo patches contained no nicotine. Active patches and placebo patches were supplied by Elan Pharmaceuticals Ltd, Athlone, Ireland. While a comparison of pharmacokinetic properties shows differences between the different brands of patches across the initial days of treatment, within 3 days all brands achieve comparable nicotine levels and maintain these throughout treatment.

Adjuvant Treatment

In the group counseling intervention used in study 1, groups of eight to 12 members met for approximately 60 minutes per week for 8 weeks. Sessions were designed to provide information in a supportive atmosphere and teach coping skills appropriate to the subjects' place in the quitting process. This was designed to be a high-intensity counseling intervention. Individual counseling in study 2 consisted of weekly meetings for 8 weeks with individual subjects. Sessions lasted 10 to 20 minutes and targeted topics relevant to the individual's place in the quit process. This counseling was designed to be a moderate-intensity counseling intervention.

Both counseling interventions stressed the importance of abstinence, along with the identification of high-risk situations and potential coping behaviors. Both counseling interventions were conducted by psychologists or psychology graduate students who followed a treatment manual developed for each study.

Statistical Analyses

Baseline subject characteristics in the two groups (active patch vs placebo patch) were evaluated with two-tailed independent-group t tests for continuous-level dependent variables; χ^2 tests of independence were computed for categorical outcome variables. For continuous variables displaying significant heterogeneity of variance, separate-variance independent-group t tests were computed. Efficacy was tested with χ^2 tests of independence. The relations among pretreatment measures of nicotine dependence and intratreatment measures (blood nicotine and cotinine levels and withdrawal severity) were evaluated with Pearson product-moment correlations. Prediction of end-of-treatment abstinence or smoking from intratreatment abstinence or smoking was examined both descriptively (by cross-tabulation) and by means of odds ratios (ORs) calculated separately for active patch subjects and placebo patch subjects in each study. Additionally, subjects classified as smoking at 6 months (relapsers) were examined to determine what percentage of subjects resumed smoking at each week of patch treatment. We use the categorical variable abstinence or smoking as our major outcome variable because it is the variable of chief clinical importance. All analyses were conducted on an intent-to-treat basis with those unavailable for follow-up or without biochemical confirmation of abstinence classified as smokers.

RESULTS

Study 1

Table 1 depicts the baseline characteristics of subjects in the active group and placebo group. No statistically significant differences were noted between the two groups. Of the 88 subjects who were enrolled and randomized, 77 completed the 8-week active treatment phase of the study. Of these, one subject in the placebo patch group used nicotine gum throughout the study and was excluded from all analyses. Of the 11 who failed to complete the active treatment phase (the first 8 weeks on study), 10 were using placebo patches, and one was using an active patch.

Efficacy

Abstinence was defined as a self-report of zero cigarettes smoked in the preceding 7 days confirmed by an expired CO_a value of less than 10 ppm. At the end of patch therapy (8 weeks), 26 active patch subjects (59.1%) were clas-

sified as abstinent, while 17 placebo patch subjects (39.5%) were abstinent ($\chi^2[df=1]=3.3$; $P=.07$). Of the 87 study subjects, biochemical confirmation of smoking status was available for 62 at the 6-month follow-up mark. Of the remaining 25 subjects, five refused to be interviewed, 11 failed to complete treatment, and nine were unavailable for follow-up. At 6 months, 15 (34.1%) of 44 active patch subjects were abstinent, compared with nine (20.9%) of 43 placebo patch subjects ($\chi^2[df=1]=1.9$; $P=.17$). Survival analyses indicated statistically significant ($P<.05$) lower relapse among active patch subjects during the 6-month follow-up period.[2]

Study 2

Table 1 depicts the baseline characteristics of subjects in the active group and placebo group. The two groups did not differ reliably on any of these characteristics. Of the 112 subjects who were enrolled and randomized, 79 completed the treatment phase of the study. Of the 33 who failed to complete the treatment phase (the first 6 weeks on study), 18 were using placebo patches, and 15 were using active patches.

Efficacy

Abstinence was defined as in study 1. At the end of patch therapy (6 weeks), 21 active patch subjects (36.8%) were abstinent, while 11 placebo patch subjects (20.0%) were abstinent ($\chi^2[df=1]=3.9$; $P=.05$). Of the 112 subjects who participated in this study, biochemical verification of self-reported smoking status was obtained for 72 at the 6-month follow-up mark. Of the remaining 40 subjects, 33 failed to complete treatment, and seven were unavailable for follow-up. At this time, 10 (17.5%) of 57 active patch subjects were abstinent, while only four (7.3%) of 55 placebo patch subjects were abstinent ($\chi^2[df=1]=2.7$; $P=.10$). Survival analysis indicated statistically significant ($P<.05$) lower relapse among active patch subjects during the 6-month follow-up period.[2]

Baseline characteristics did not differ reliably across the two studies. The difference in attrition and efficacy seen between the two studies is hypothesized to be related to the nature of the adjuvant treatments (eg, group vs individual counseling and length of treatment sessions).

Pretreatment Measures

Baseline expired CO_a level, blood nicotine and cotinine levels, cigarettes smoked per day, number of years smoked, and Fagerstrom Tolerance Questionnaire score were assessed in relation to end-of-treatment abstinence and 6-month abstinence. Point-biserial correlations were conducted separately for active patch subjects and placebo patch subjects for each of these variables. None of these pretreatment measures showed a consistent relationship with posttreatment success across studies 1 and 2. None of the 32 correlations was statistically significant, and none exceeded −.26.

Table 1.—Baseline Subject Characteristics for Study 1 and Study 2*

Variable	Study 1		Study 2	
	Active Patch (n=44)	Placebo Patch (n=43)†	Active Patch (n=57)	Placebo Patch (n=55)
Age, y	43.3 (1.5)	42.6 (1.4)	43.1 (1.2)	44.2 (1.5)
Female gender, %	56.8	55.8	68.4	67.3
Cigarettes per day	28.3 (1.1)	30.3 (1.5)	29.8 (1.3)	30.8 (1.3)
Expired air carbon monoxide level, ppm	32.3 (1.8)	31.4 (2.6)	32.5 (1.8)	34.3 (1.6)
Nicotine, ng/mL	21.0 (1.1)	18.7 (1.0)	21.0 (1.3)	21.4 (1.1)
Cotinine, ng/mL	328.2 (18.4)	281.6 (16.5)	311.3 (16.6)	311.4 (14.4)
Years smoking	25.2 (1.3)	24.3 (1.4)	24.3 (1.2)	25.9 (1.4)
Fagerstrom Tolerance Questionnaire score	7.3 (0.2)	6.9 (0.2)	7.2 (0.2)	7.7 (0.2)
Weight, kg	79.3 (2.3)	80.1 (3.2)	72.9 (2.3)	72.5 (2.3)
Beck Depression Inventory score[14]	5.1 (0.7)	5.3 (0.7)	6.3 (0.8)	6.2 (0.8)

*Standard errors are in parentheses. No group differences were significant ($P>.05$) in either study.
†One subject in the placebo patch group chewed nicotine gum throughout the patch treatment phase of the study. This subject was eliminated from all analyses.

Table 2.—Correlations Between Baseline, Week 1, and Week 4 Withdrawal Severity and Abstinence at End of Treatment and 6 Months*

Withdrawal	Study 1				Study 2			
	Abstinence at 8 Weeks		Abstinence at 6 Months		Abstinence at 6 Weeks		Abstinence at 6 Months	
	Active Patch	Placebo Patch	Active Patch	Placebo Patch	Active Patch	Placebo Patch	Active Patch	Placebo Patch
Baseline	−.36† (40)	.08 (36)	−.36† (40)	.04 (36)	.18 (49)	−.19 (49)	.06 (49)	−.20 (49)
Week 1	−.38‡ (44)	.18 (40)	−.42‡ (44)	.15 (40)	−.02 (56)	−.13 (53)	−.04 (56)	−.13 (53)
Week 4	−.35† (43)	−.25 (34)	−.35† (43)	−.05 (34)	−.19 (51)	−.26 (38)	−.17 (51)	−.21 (38)

*Higher scores on the withdrawal measure indicate greater withdrawal symptoms. Abstinence variables are coded: 1 indicates abstinence; and 0, smoking. The number of subjects on which correlation was based is in parentheses. The number changed as a function of the availability of usable withdrawal ratings.
†$P<.05$.
‡$P<.01$.

Intratreatment Measures

Precessation serum nicotine and cotinine levels have been proposed as measures of tobacco dependence and as determinants of successful smoking cessation.[15] Additionally, the degree to which pretreatment serum nicotine and cotinine levels are matched or maintained via replacement therapy may be important in determining cessation success.[16]

To examine these relations, we compared the following three measures of nicotine and cotinine with successful smoking cessation outcome among active nicotine patch users: (1) baseline blood nicotine and cotinine levels, (2) absolute blood nicotine and cotinine levels achieved during nicotine replacement treatment (as measured at week 4 of patch treatment), and (3) percentage of baseline blood nicotine and cotinine levels replaced with nicotine replacement therapy. These point-biserial correlations revealed no consistent relation with outcome. For instance, the only significant predictor of 6-month abstinence was baseline nicotine level in study 2 (point-biserial correlation=−.27) (higher baseline nicotine levels were associated with 6-month relapse). The same correlation was small and opposite in sign for study 1 (point-biserial correlation=.19).

Finally, we assessed whether the severity of withdrawal symptoms during treatment was correlated with successful cessation. A withdrawal severity index was constructed by calculating the mean score for the daily eight-item withdrawal scale. Withdrawal severity at baseline, week 1, or week 4 after quitting did not consistently correlate with abstinence (Table 2). To assess the possibility that some of these intratreatment measures were confounded by intratreatment smoking, we separately analyzed data of subjects who were completely abstinent; none of the correlations was significant.

Intratreatment Smoking

In contrast to the measures described herein, intratreatment smoking did demonstrate a consistent relationship with posttreatment success. Specifically, we analyzed the relation between intratreatment smoking by week and post-

Table 3.—Smoking in Weeks 1 and 2 of Patch Treatment and Abstinence Status at End of Treatment and 6 Months in Active Patch Subjects

	Study 1, Active Patch Subjects (n=44)			Study 2, Active Patch Subjects (n=57)		
Abstinent in Week	No. of Subjects	Abstinence at End of Treatment, %	Abstinence at 6 Months, %	No. of Subjects	Abstinence at End of Treatment, %	Abstinence at 6 Months, %
1	27	77.8	40.7	23	65.2	39.1
2	26	76.9	46.2	22	72.7	40.9
1 and 2	22	81.8	45.5	16	75.0	50.0
Smoking in Week	**No. of Subjects**	**Smoking at End of Treatment, %**	**Smoking at 6 Months, %**	**No. of Subjects**	**Smoking at End of Treatment, %**	**Smoking at 6 Months, %**
1	17	70.6	76.5	34	82.4	97.1
2	18	66.7	83.3	35	85.7	97.1
1 or 2	22	63.6	77.3	41	78.0	95.1

Table 4.—Smoking in Weeks 1 and 2 of Patch Treatment and Abstinence Status at End of Treatment and 6 Months in Placebo Patch Subjects

	Study 1, Placebo Patch Subjects (n=43)			Study 2, Placebo Patch Subjects (n=55)		
Abstinent in Week	No. of Subjects	Abstinence at End of Treatment, %	Abstinence at 6 Months, %	No. of Subjects	Abstinence at End of Treatment, %	Abstinence at 6 Months, %
1	13	76.9	38.5	12	50.0	8.3
2	16	81.3	43.8	10	70.0	30.0
1 and 2	12	83.3	41.7	5	60.0	0
Smoking in Week	**No. of Subjects**	**Smoking at End of Treatment, %**	**Smoking at 6 Months, %**	**No. of Subjects**	**Smoking at End of Treatment, %**	**Smoking at 6 Months, %**
1	30	76.7	86.7	43	88.4	93.0
2	27	85.2	92.6	45	91.1	97.8
1 or 2	31	77.4	87.1	50	84.0	92.0

treatment cessation success. These analyses demonstrated that smoking during any week of treatment was highly and negatively associated with successful cessation.

Because it would be most useful clinically to predict long-term outcomes early in the quitting process, three time periods from the initial phase of treatment were analyzed intensively. These were (1) any smoking in the first week of treatment, (2) any smoking in the second week of treatment, and (3) any smoking in either the first or second week of treatment. Tables 3 and 4 show the relation of intratreatment smoking on short-term and long-term smoking cessation rates using these three predictor time periods. Any smoking during the first 2 weeks of treatment was highly associated with a poor prognosis. However, smoking or abstinence during week 2 was the most accurate predictor of outcome (Table 5).

Table 3 illustrates the relation between early intratreatment smoking and clinical success at the end of treatment and the 6-month follow-up mark among active nicotine patch users for each study. Smoking was defined as any tobacco use at a given time point. Among nicotine patch users, if a patient smoked at all during week 2, there was a 66.7% chance or 85.7% chance (studies 1 and 2, respectively) that the patient would be smoking at the end of treatment. This relationship was also predictive for long-term outcomes. If a patient smoked in week 2, there was an 83.3% chance or 97.1% chance (studies 1 and 2, respectively) that the patient would be smoking 6 months later. Similar findings were noted among placebo patch users (Table 4). Among placebo patch users, if a patient smoked during week 2, there was an 85.2% chance or 91.1% chance (studies 1 and 2, respectively) that the patient would be smoking at the end of treatment and a 92.6% chance or 97.8% chance (studies 1 and 2, respectively) that the patient would be smoking 6 months later.

Abstinence during week 2 was also highly predictive of both short-term and long-term abstinence. For example, among active nicotine patch users, if a patient were totally abstinent during week 2, there was a 76.9% chance and 72.7% chance (studies 1 and 2, respectively) that the patient would be abstinent at the end of treatment and a 46.2% chance and 40.9% chance (studies 1 and 2, respectively) that the patient would be abstinent 6 months later (Table 3). Among placebo patch users, if a patient were totally abstinent during week 2, there was an 81.3% chance and 70.0% chance (studies 1 and 2, respectively) that the patient would be abstinent at the end of treatment and a 43.8% chance and 30.0% chance (studies 1 and 2, respectively) that the patient would be abstinent 6 months later (Table 4).

We examined the issue of whether amount of smoking in week 2 added to the predictive validity of our prediction rule. The results of a variety of analyses suggested that including information about the amount of smoking did not alter the predictive accuracy of the rule. Another test of the accuracy of a prediction rule is to determine the proportion of treatment failures the rule identifies—ie, of all subjects smoking at follow-up, what percentage smoked by week 2? Among active nicotine patch users in studies 1 and 2, respectively, of those smoking at 6 months, 59% and 83% had first smoked by the end of week 2 (74% across both studies; Figure). Among placebo patch users in studies 1 and 2, respectively, of those smoking at 6 months, 79% and 90% had first smoked by the end of week 2 (86% across both studies; Figure).

Odds ratios constitute another index of association between early smoking and long-term outcome and reflect the classification power of a prediction rule (ratio of correct to incorrect decisions yielded by the prediction rule). When smoking in week 2 of treatment was used as a marker for outcome among nicotine patch users, successful prediction was greatly enhanced at end of treatment (OR, 6.7 and 16.0 for studies 1 and 2, respectively) and at six months (OR, 4.3 and 23.5 for studies 1 and 2, respectively) (Table 5). Although smoking during any time within the first 2 weeks is predictive of failure to quit, the ORs demonstrate that the week 2 rule is associated with the most accurate predictions and the least number of misclassifications. The power of the week 2 rule to detect the observed association with 6-month outcome was .53 in study 1 and .95 in study 2. Similar findings are ob-

served when the ORs are calculated for placebo patch subjects (Table 5). Additionally, ϕ coefficients (a correlation coefficient for two dichotomous variables) of the decision rule for each time point were statistically significant.

Finally, we recomputed the ORs after statistically controlling for a variety of other potential predictor variables. In particular, we examined the relation between week 2 smoking and abstinence, both at end of treatment and at 6-month follow-up, after controlling for measures of physical dependence (Fagerstrom Tolerance Questionnaire score, pretreatment blood nicotine level, number of cigarettes smoked pretreatment, and pretreatment expired CO_a level) and withdrawal during the first week of treatment. These analyses revealed that in all cases the adjusted ORs were actually higher than the respective unadjusted ORs.

Prediction of Week 2 Smoking

Because smoking abstinence in week 2 was such an accurate predictor of long-term success, we performed simultaneous logistic regression analyses to identify predictors of week 2 smoking. In particular, we examined the relation of week 2 smoking and a variety of other predictor variables: withdrawal severity of week 1, pretreatment Fagerstrom Tolerance Questionnaire score, pretreatment blood nicotine level, pretreatment expired CO_a level, and mean number of cigarettes smoked daily at pretreatment. These analyses revealed that no variable predicted week 2 smoking in study 1, but two did in study 2: pretreatment Fagerstrom Tolerance Questionnaire score and pretreatment blood nicotine level. However, their level of association with week 2 smoking was low, with no r value exceeding .19. Therefore, no variable consistently and significantly predicted week 2 smoking across both studies 1 and 2, and when associations were found, they were low.

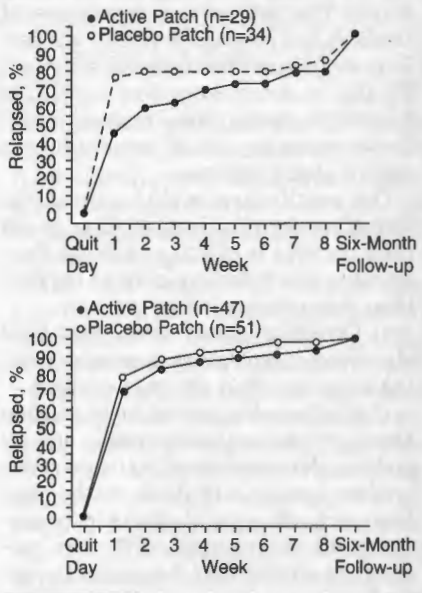
COMMENT

The intent of this research was to identify a simple yet powerful prediction rule that could be used easily in a clinician's office to predict smoking cessation success or failure with or without the nicotine patch. Analyses were based on two separate studies, using two independent samples of smokers, two different adjuvant counseling therapies, and active patch therapy vs placebo patch therapy. In this way these two studies provide an opportunity to test the generalizability of our findings.

The analyses reveal one powerful prediction rule for clinicians: any smoking in the first 2 weeks of treatment predicts both short-term and long-term failure, with week 2 smoking being particularly predictive of outcome (Table 5). Conversely, total abstinence during the first 2 weeks of treatment was consistently correlated with sustained smoking cessation success. By assessing the presence or absence of any smoking during the second week of treatment, clinicians can predict with good accuracy whether the patient will or will not quit smoking. Early detection of high-risk patients may also allow the clinician to modify treatment to increase the likelihood that at-risk patients will succeed.

These analyses also identified a number of factors that did not consistently predict smoking cessation outcome. Specifically, these analyses cast some doubt on the ability of numerous accepted or hypothesized measures of tobacco dependence to predict success or failure consistently for patients using the nicotine patch.[17] Baseline indicators, such as the number of cigarettes smoked per day, Fagerstrom Tolerance Questionnaire score, and years of smoking, were poorly and inconsistently correlated with successful cessation. Biochemical measures also fared poorly as predictors: pretreatment expired CO_a value, pretreatment blood nicotine and cotinine levels, absolute blood nicotine and cotinine levels achieved on the nicotine patch, and the percentage replacement of pretreatment nicotine or cotinine with nicotine patch therapy were poorly and inconsistently correlated with successful smoking cessation. These measures might have shown significant relations with outcome had we had many more subjects in our two studies, but we do not believe that this would change the relative superiority of the week 2 rule to predict outcome.

Our current analyses failed to identify an easy-to-use clinical measure to identify a priori (ie, before treatment begins) smokers who are most likely to succeed or fail with or without the nicotine patch. One caveat to keep in mind is that our results may merely reflect unreliable assessment or the selection of improper measures of



The cumulative proportion of subjects smoking at 6-month follow-up for study 1 (top) and study 2 (bottom), presented as a function of the week at which they smoked their first cigarette (ie, when relapsers started to smoke).

Table 5.—Odds Ratios (ORs), 95% Confidence Intervals (CIs), and ϕ Coefficients for Smoking in Weeks 1 and 2 and Abstinence Status at End of Treatment and 6 Months in Active Patch Subjects and Placebo Patch Subjects

	Study 1				Study 2			
	End of Treatment		6 Months		End of Treatment		6 Months	
Week	Active Patch (n=44)	Placebo Patch (n=43)	Active Patch (n=44)	Placebo Patch (n=43)	Active Patch (n=57)	Placebo Patch (n=55)	Active Patch (n=57)	Placebo Patch (n=55)
1								
OR (95% CI)	8.4 (2.1-33.5)	11.0 (2.3-51.2)	2.2 (0.6-8.7)	4.1 (0.88-16.9)	8.8 (2.6-29.9)	7.6 (1.8-32.9)	21.2 (2.5-183.7)†	1.2 (0.1-12.8)
ϕ coefficient	.48*	.50*	.16	.28	.48*	.39*	.47*	.02
2								
OR (95% CI)	6.7 (1.7-25.4)	24.9 (4.8-129.0)	4.3 (1.0-18.5)	9.7 (1.7-55.7)	16.0 (4.2-60.7)	23.9 (4.4-130.7)	23.5 (2.7-204.6)	18.9 (1.7-207.8)
ϕ coefficient	.44*	.66*	.31†	.43*	.59*	.59*	.48*	.41*
1 or 2								
OR (95% CI)	7.9 (2.0-31.6)	17.1 (3.0-97.3)	2.8 (0.8-10.4)	4.8 (1.0-22.8)	10.7 (2.8-41.2)	7.9 (1.1-54.9)	19.5 (3.5-109.6)	1.1 (1.0-1.2)
ϕ coefficient	.46*	.56*	.24	.31†	.49*	.32†	.53*	.09

*$P<.01$.
†$P<.05$.

dependence. We believe our biochemical confirmation of outcomes, our use of recognized assessment instruments, and the broad array of dependence measures argue against these possibilities. Another caveat is that a restriction of range influenced our results. Our samples consisted of moderately to heavily dependent smokers; a wider inclusive sampling of the dependence continuum may have shown a stronger relationship between outcome and measures of dependence. Moreover, these results may be most relevant to the 24-hour nicotine patches that are used by 90% of the current patch users. Additionally, all our subjects received supportive counseling. Predictive relations might differ for self-quitters vs those in formal treatment programs. Finally, our inability to identify a clinically useful a priori measure may reflect the heterogeneity of smokers in the United States attempting to quit. That is, there may be subtypes of smokers, and no single predictor will perform well across these different subtypes. Finally, as our smokers were enrolled in a university-based clinical research study, these results may not be as powerful in a typical clinic population.

Our results do provide important information for clinicians seeking to aid their patients in quitting smoking. Specifically, the following clinical implications deserve emphasis:

1. Clinicians should stress that total abstinence is central to a successful smoking cessation effort for most smokers.

Optimal smoking cessation counseling should emphasize the importance of early and complete abstinence. Across our two studies, among individuals on the nicotine patch who were abstinent in the second week of treatment, 47% were successfully abstinent at 6 months. In contrast, among individuals who smoked at all in the first 2 weeks of treatment, only 11% were abstinent at 6 months. Most smokers who have previously tried to quit are already aware of the danger of any smoking and provide anecdotal support for this clinical rule. A common report among smokers who had previously relapsed is that they thought they could have a cigarette "now and then" only to quickly relapse to prequit smoking levels.[18] Hall and colleagues[19] have found that those individuals holding a strict abstinence orientation are more likely to achieve long-term success.

2. Clinicians should "front load" smoking cessation counseling and support during the first 2 weeks after quitting.

Among the subset of our patients using the active nicotine patch, 74% of those who ultimately relapsed by 6 months began smoking in the first 2 weeks. Among placebo patch patients who had relapsed by 6 months, 86% began smoking in the first 2 weeks. Clinicians need to provide support and counseling during this critical period of high relapse. For this reason, clinicians should schedule a follow-up visit in person or make contact by telephone[20] during the important first 2 weeks after quitting; review of coping strategies and the importance of total abstinence should be emphasized during this contact.

3. Assess smoking during the second week after the quit attempt to predict smoking cessation outcome.

Smoking during any portion of the treatment period predicted a poor outcome. However, we recommend using any smoking during week 2 as a predictor of outcome because it occurs early in the quit attempt and requires the determination of abstinence for only a brief period of time. Importantly, it is an easy-to-use prediction rule for clinicians: follow-up with the patient in person or by telephone during the second week of a quit attempt—if the patient has smoked at all during this time period, consider an alteration of treatment. More research may result in refinement of this prediction rule, but in our studies, any smoking indicated heightened risk for eventual relapse.

While our results suggest a reliable prediction rule, they do not reveal how treatment should be altered if patients smoke during the first 2 weeks of treatment. Our clinical experience suggests that if a patient is smoking in the second week of treatment, the clinician could consider offering the patient more intensive pharmacotherapy and/or additional adjuvant therapy (perhaps referral to a formal cessation program). However, our clinical experience suggests that these steps should be taken only if the patient is still motivated to stop smoking. If the patient reports feeling discouraged or defeated, treatment may be temporarily withdrawn, allowing the clinician and patient to jointly select a new, future quit date. Obviously, more research is needed to determine appropriate treatment alterations and responses to early failure.

Finally, our results point to two other research needs: first, research aimed at the identification and evaluation of smoker subtypes so that treatment and prediction can be tailored to the individual and second, the feasibility of a graded, stepped-care approach to intervention should be determined.[21] This is the approach used for many medical disorders, such as hypertension or hyperlipidemia, where dose or other dimensions of treatment are increased only when an individual fails to respond to previous treatment. If a similar approach proves effective with smoking cessation, it would serve as a model for clinicians as they combat this devastating chronic disease.[22]

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