Effectiveness of the Nicotine Inhaler for Smoking Cessation in an OTC Setting

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***Objective*: To evaluate the effectiveness of the Nicotrol® nicotine inhaler as an aid to smoking cessation in over-the-counter (OTC) versus health-care-provider (HCP) conditions. *Methods*: Five hundred twenty healthy smokers were randomized to the treatment conditions and followed for a year. *Results*: At most follow-up visits, abstinence rates for the HCP group were 2 to 3 times those observed in the OTC group. Abstinence at 1 year was .77% in the OTC condition versus 3.08% in the HCP condition [P<.01]. Inhaler use was low. *Conclusions*: OTC nicotine inhaler appears to be ineffective, though quit rates are improved with HCP assistance.**

***Key words*: smoking cessation, OTC, nicotine inhaler, nicotine replacement**

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Despite numerous achievements in tobacco control over the past decade, prevalence of smoking in the United States has only gradually declined since 1990 (approximately 25.7% for men and 21.5% for women in 1999).[1,2] It is estimated that more than 70% of smokers in the United States have tried to quit at least once, and approximately 46% will attempt to quit each year, though most such efforts are unsuccessful.[3] Meta-analyses strongly suggest that nicotine replacement therapies including nicotine gum, patch, nasal spray, and inhaler all approximately double the likelihood of abstinence (OR 1.5-2.7), and they should be recommended as first-line treatments for nicotine dependence.[3] However, these odds ratios are based on studies completed in study environments that are most similar to prescription, not OTC, use.

Both nicotine patch and nicotine gum have been approved as OTC medications. Meta-analyses of OTC efficacy have been completed only for nicotine patch, and these analyses found that odds ratios clearly favored nicotine patch over placebo.[3,4] However, there has been substantial methodological variability across such investigations. For example, only 2 OTC studies of the nicotine patch required participants to pay for medication[5,6] – even though most users of OTC medication must purchase these medications themselves. Furthermore, despite efforts to minimize behavioral support, some "OTC"

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studies required participants to attend up to 6 visits in the first 6 weeks of treatment,[6,7] thus making it unclear whether these studies truly reflect a real-world OTC environment. Because there are data to suggest that the placebo effect may be substantial in smoking cessation studies[8] and that number of visits alone may positively affect quit rates,[3] studies demonstrating the efficacy of OTC medications need to be considered with caution.

In fact, not all studies have found nicotine patch effective in an OTC environment.[5] The Leischow et al[5] study compared OTC with a health-care-provider intervention and did not include a placebo group. It also included few scheduled visits and required participants to pay for medications. That study found 1-year quit rates under 5% in the OTC group, which is comparable to self-help quit rates.[9,10] Indeed, in a recent meta-analysis of OTC NRT studies, 6-month quit rates averaged 7%, which is just 1% higher than the 6% quit rate found in a meta-analysis of self-quit rates.[4] Furthermore, 2 analyses of state surveillance data have failed to demonstrate the effectiveness of OTC NRT.[11,12] Thus, given the mixed results of studies assessing OTC NRT, additional research is needed in order to help consumers determine which treatments will best benefit them in their smoking cessation attempt.

The nicotine inhaler has been shown to be both safe and efficacious in clinical trials.[3,13] However, sales and estimated use of the inhaler have lagged behind the patch and gum, indicating potential barriers to access or market penetration – possibly because the nicotine inhaler has remained a prescription product.[1] In light of the established efficacy and safety of the nicotine inhaler in clinical settings that include behavioral support, and in response to the need for further evaluation of NRT use in OTC settings, the current study was conducted. The primary purpose was to evaluate the effectiveness of the nicotine inhaler as an aid to smoking cessation in an over-the-counter simulation in comparison to a health-care-provider (HCP) condition. In addition, impact of individual participant characteristics such as demographics, health status, withdrawal symptoms, craving, mood, quality-of-life changes, alcohol consumption, and medication use were assessed. This paper will focus on efficacy results, medication use, and subject characteristics predicting cessation.

METHODS

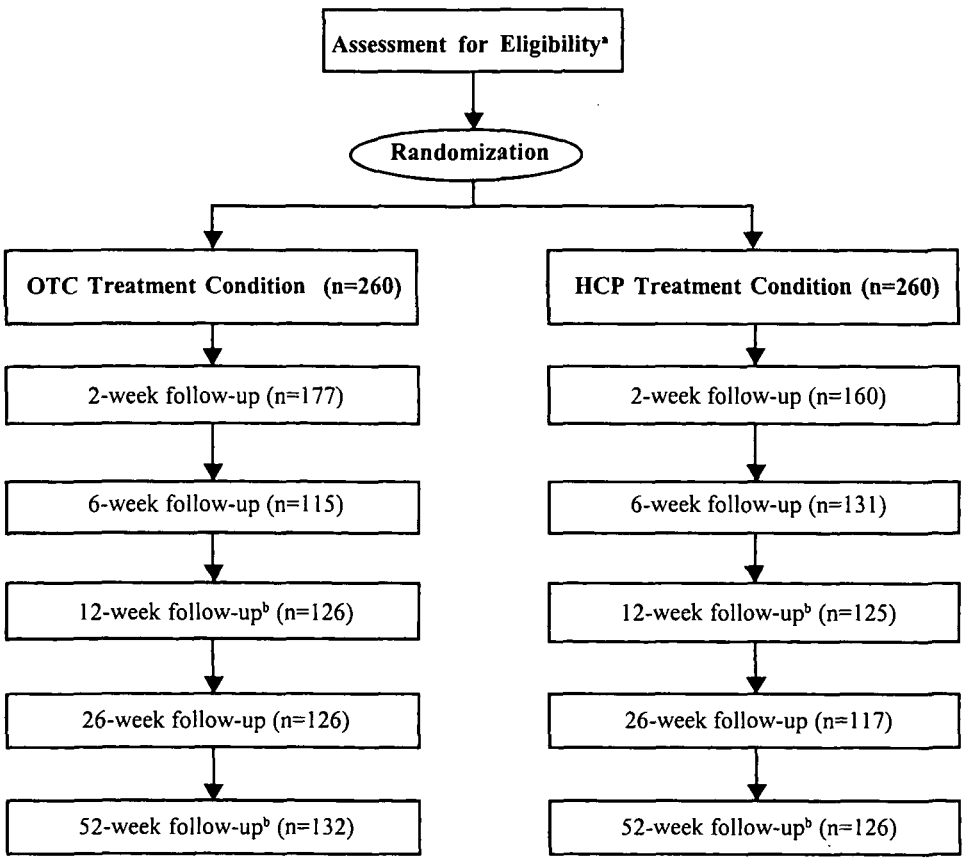
Subject Recruitment, Screening, and Randomization

Methods were similar to those used in an earlier study.[5] Participants (n=520) were recruited as part of a larger recruitment effort for multiple studies, through local print and broadcast media, and could potentially have been eligible for more than one study. Figure 1 depicts study flow and subject participation. No unique identifiers were used at the initial stages of recruitment; therefore, it was not possible to ascertain the number of individuals assessed for eligibility. Advertisements announced the availability of a smoking cessation research program and provided the study telephone number for interested individuals. No formal telephone screening was conducted; only information regarding the study site and criteria for eligibility were provided over the phone. Interested persons were invited to an on-site screening evaluation at the study research clinic, at which time they were asked to complete brief smoking status, health history, and demographic questionnaires to determine eligibility to purchase medication (including a health-care-provider contact, if necessary).

Eligible participants were 18 years of age or older, self-reported chronic smokers, available for the duration of the study, and able and willing to complete study requirements (including willingness and intent to purchase study medication) as indicated by their signing informed consent. Participants were excluded if they had experienced a heart attack or CVA (cerebrovascular accident) within the last 3 months, had a current diagnosis of unstable angina or irregular heart rate, any history of allergy to nicotine, menthol, or any inhaler constituents, or if they had any other medical conditions deemed unacceptable by the study health-care provider. Women who were pregnant or breastfeeding, or who reported not using a medically approved form of birth control and were unwilling to do so, were also excluded. Those already enrolled in a nicotine replacement study were excluded, and no 2 members of the same household were eligible to participate.

Participants were then asked to read

Figure 1
Participant Flow and Follow-up



Note.
a No unique identifiers were used at the initial stages of recruitment; therefore it was not possible to ascertain the number of individuals assessed for eligibility.
b Visits for week 12 and 52 were conducted via telephone. If abstinence was reported at week 52, an on-site CO verification was scheduled.

the package insert for the nicotine inhaler and were advised to consult a primary care physician if they had any contraindicatory medical conditions prior to purchasing the medication. Participants were advised of medication cost and asked to indicate in writing their intent to purchase and use this medication. Additionally, participants were provided as part of the study consent form, descriptions of both of the treatment conditions to which they could be assigned. Informed consent was then obtained, and breath carbon monoxide levels were assessed.

Participants were then assigned to 1 of 2 treatment conditions: (a) over-the-counter or (b) health-care provider. A computer-generated random-allocation sequence was created by the study statistician and provided to staff conducting screening appointments with participants. Each participant entering the study was given the next available number and was informed of the group assignment.

Medication Purchase and Treatment Interventions

OTC condition. Participants in the OTC condition were allowed to purchase medications immediately after being randomized to that condition, but were required to make their first medication purchase within 4 weeks after becoming eligible to participate in the study. Participants were instructed to use the nicotine inhaler for up to 3 months. Medication purchases could, however, occur at ad libitum intervals for up to 26 weeks following the initial medication purchase, as per study instructions and consent form guidelines. At first purchase, participants were scheduled for a 2-week follow-up visit (allowing for a 7-day scheduling window). Participants who did not purchase medication within the first 4 weeks were excluded from the study and were followed up to determine the reason for failure to purchase medication.

Instruction on how to use the nicotine inhaler was provided via package insert. In addition, the research program phone number was provided to answer questions about the inhaler and local community tobacco-cessation resources. Study staff provided no personalized behavioral treatment materials or advice to the over-the-counter group.

Health-Care-Provider Condition

Eligibility to purchase in the HCP group began only after participants attended a brief appointment with a study health-care provider. There is a legal responsibility for an approved health care provider to determine medical eligibility to use a prescription medication, unlike with OTC medications. Thus, those subjects assigned randomly to the HCP condition were assessed for eligibility to use the medication as would be the case in the real world. The methods adopted in this protocol are virtually the same as those used by pharmaceutical companies to test their medications for OTC use.

This appointment was scheduled within 2 weeks of the initial screening visit and conducted by a nurse practitioner experienced in providing smoking cessation treatment. Participants' medical eligibility for the study was confirmed at this appointment. In addition, brief psychosocial behavioral counseling and a smoking cessation pamphlet was provided along with instructions for inhaler use and a prescription for the nicotine inhaler.

The health-care provider was trained to deliver approximately 10 minutes of smoking cessation counseling. Instruction on proper use of the inhaler, personalized advice to quit related to the subject's medical history, and a brief review of the NCI patient education booklet *Clearing the Air: How to Quit Smoking... and Quit for Keeps* were given and discussed at that time. Special attention was given to sections of the booklet most relevant to the individual subject's concerns about quitting. Content and duration of the HCP's behavioral counseling (eg, setting target quit day, problem solving, discussing of personal triggers for smoking) were recorded at the time of the visit. Additionally, duration of discussion specifically addressing inhaler-use guidelines was recorded.

Upon determination of medical eligibility and behavioral counseling, participants were provided with a prescription for a 1-month supply of medication (4 boxes or 168 inhalers), with 2 one-month refills, which was only valid at the simulated OTC site. Requirements for first medication purchase were identical to the OTC condition (eg, purchase within 4 weeks). At first purchase, participants were scheduled for a 2-week follow-up visit (allowing for a 7-day scheduling window). If participants wished to continue medication beyond 3 months, they were required to speak to the health-care provider to request an additional prescription for up to a total of 26 weeks.

Neither treatment condition required participants to set a quit date or to be abstinent from smoking to purchase medication (although medication labeling encourages abstinence). The cost of each box of Nicotine Inhalers (7 trays with 6 cartridges per tray) was $20.00. Each 10-mg nicotine inhaler cartridge delivers approximately 5 mg of nicotine for inhalation.

Follow-Up

For both treatment groups, follow-up appointments were conducted at weeks 2, 6, 12, 26, and 52. Weeks 2, 6, and 26 were held at the study site, whereas weeks 12 and 52 were completed via telephone. Research assistants attempted to contact all study participants at week 52, except those who had specifically withdrawn consent, regardless of prior reported smoking

status. This was done out of concern that inadequate follow-up in an earlier OTC study[5] might have resulted in failure to detect abstinent study participants. If abstinence was reported at week 52, an on-site CO verification visit was scheduled. Those who attended this visit were compensated $10.00 for travel expenses. For both conditions, at scheduled follow-ups as well as unscheduled medication purchase visits, information was collected on (a) smoking status and smoking patterns (the latter if the subject was still smoking), (b) adverse events, (c) concomitant medication use, (d) nicotine inhaler use, (e) mood changes, and (f) alcohol consumption.

Self-reported continuous abstinence and breath carbon monoxide of CO<9ppm between weeks 2 and 6 were primary determinants of smoking cessation success.

Analytic methods. Preliminary analysis using t-tests, tests of proportions, rank-sum and chi-squared tests compared sociodemographic characteristics and levels of nicotine dependence across experimental groups to confirm successful randomization.

Continuous abstinence was defined as no smoking at any time after the 2-week follow-up visit and point prevalence abstinence was defined as no smoking within 7 days of any visit. Tests of proportions were used in the cross-sectional comparisons of continuous and point prevalence abstinence rates. Cross-sectional quit rates were calculated using intent-to-treat criterion (ie, all eligible participants were included in the analysis). The intent-to-treat analysis that includes all participants, regardless of whether or not they actually purchased medication, is the most conservative definition and the one that has been used by the FDA when determining efficacy of a smoking cessation medication. Participants who missed visits were treated as smoking, as were participants claiming abstinence for which CO verification was not obtained.

Cross-sectional analyses are comparable to previous literature but do not fully use the statistical power available in longitudinal data. Therefore, longitudinal analysis of point prevalence abstinence was conducted following the recommendations from a recent methodology conference sponsored by the Society for Research on Nicotine and Tobacco.[14] A generalized estimating equation (GEE) approach was used, taking advantage of information provided by multiple measurements while accounting for nonindependence of repeated measures by explicitly modeling the correlation matrix for error terms.[15] The GEE model incorporated a logistic link function to accommodate the dichotomous outcome, and the resulting coefficients here have the same interpretation as occurs with ordinary logistic regression analysis.

GEE models accommodate missing data with some loss of statistical power but no bias if the data are missing at random.[16] Moreover, pattern-mixture models have been developed to account for a portion of bias due to nonrandom missing patterns.[17] Accordingly, 2 sets of GEE models were developed. The first set treats missed visits or missing CO verification as missing data, whereas the other set, like cross-sectional analysis, treats such cases as smoking.

RESULTS

Demographics

Table 1 displays demographic characteristics assessed at the initial screening by treatment group for the entire sample. Mean age was 47.7, 51% were female, average cigarettes per day was 25.8, and the mean Fagerström score of 6 suggests that the average subject was dependent on nicotine. There were no significant differences at the .05 level between the 2 treatment groups for any of the demographic variables except for self-efficacy at 24 hours (P=.03), a measure of how confident participants were that they could quit using tobacco for at least 24 hours. Confidence levels were higher in the OTC group. Moreover, baseline cigarettes per day and Fagerström scores were marginally (P<.10) higher in the HCP than the OTC group.

Content and intensity of HCP behavioral intervention. The mean duration of behavioral counseling in the HCP group was 8.2 (+/-4.6) minutes. Of the 116 HCP participants for whom data are available, 46.6% discussed inhaler use with the health-care provider. The average duration of discussion about inhaler use was 5.2 (+/- 3.5) minutes.

Inhaler Purchases and Use

Analyses of the inhaler purchase data were completed only for the subgroup that purchased medications at least once.

Table 1
Demographic Characteristics of All Randomized Subjects (Intent to Treat)

Variable	Entire sample N	Entire sample Mean	Entire sample SD	OTC N	OTC Mean	OTC SD	HCP N	HCP Mean	HCP SD	P
Screening carbon monoxide	513	27.07	12.41	258	26.90	12.65	255	27.25	12.20	0.61[a]
Age	514	47.71	12.39	259	47.05	12.21	255	49.39	12.60	0.22[b]
Male	515	0.493	--.--	260	0.462	--.--	255	0.526	--.--	0.16[c]
White	520	0.898	--.--	260	0.892	--.--	260	0.904	--.--	0.77[c]
Educ years	511	14.23	2.40	257	14.35	2.35	254	14.11	2.45	0.27[d]
Baseline Cig	514	25.80	11.84	259	24.88	11.46	255	26.74	12.17	0.09[d]
Years Smoked	514	30.01	12.70	259	29.24	12.33	255	30.80	13.04	0.16[b]
Pack years	513	23.75	9.98	259	23.05	9.43	254	24.46	10.48	0.12[d]
Fagerstrom	509	6.01	2.38	257	5.82	2.37	252	6.20	2.38	0.07[b]
Quit attempts	499	8.34	14.81	249	8.53	15.06	250	8.15	14.58	0.39[d]
Motivation to quit	515	4.6	0.64	260	4.62	0.61	255	4.57	0.68	0.53[a]
Self-Efficacy 24 hrs.	515	4.02	1.07	260	4.12	1.01	255	3.91	1.12	0.03[a]
Expectancy 1 year	515	4.07	1.01	260	4.10	0.99	255	4.04	1.03	0.61[a]

Note.
a Wilcoxon Rank-Sum Test
b t-test
c Fisher's Exact Test
d t-test on transformed data

Table 2 displays the total number of inhaler boxes purchased and the total number of purchase visits, which did not differ between the 2 treatment groups. The average number of boxes purchased over 26 weeks was 3.2, although there was considerable variability. The maximum number of boxes purchased at a single visit was 12. The maximum number of boxes purchased over the 26-week treat-

Table 2
Inhaler Purchases and Use

Variable	Entire sample N	Entire sample Mean	Entire sample SD	OTC N	OTC Mean	OTC SD	HCP N	HCP Mean	HCP SD	P
Purchased at all	520	89.4%	--.--	260	91.9%	--.--	260	86.9%	--.--	0.09[a]
Boxes of cartridges purchased[b]	465	3.20	4.03	239	3.26	4.28	226	3.15	3.74	0.54[c]
Daily cartridges used, Visit 2	335	2.64	1.90	175	2.66	2.01	160	2.61	2.01	0.83[c]
Daily cartridges used, Visit 3	242	2.25	1.95	111	2.23	2.10	131	2.27	1.82	0.49[c]
Overall daily cartridges used in first 6 months	395	1.86	1.74	206	1.84	1.68	189	1.89	1.80	0.93[c]

Note.
a Fisher's Exact Test
b Over 26-week treatment phase
c Wilcoxon Rank-Sum test

Table 3
Co-verified Point Prevalence and Continuous Abstinence

	Co-verified Continuous Abstinence		Co-verified Point Prevalence of Abstinence	
Week	%OTC (n)	%HCP (n)	%OTC (n)	%HCP (n)
2	6.92 (18)	13.46* (35)	11.15 (29)	21.54*** (56)
6	3.85 (10)	10.77** (28)	10.77 (28)	20.77** (54)
26	1.54 (4)	4.62* (12)	6.15 (16)	11.54* (30)
52	0.77 (2)	3.08 (8)	3.08 (8)	8.46** (22)

Note.
*P<.05; **P<.01; ***P<.001
Intent to treat
Missing=smoking
Self-reported abstinence with missing CO verification = smoking

ment phase was 26.

Table 2 also presents average daily use of inhalers as reported at scheduled visits at week 2, week 6, and an average over the first 26 weeks of the study combining information from visits at weeks 2, 6, 12, and 26. At no time did inhaler use differ significantly by group; however, use did decline over time across both groups. As with the numbers of boxes purchased, there was considerable variability in number of inhalers used per day, with a range of 0 to 10.

Cross-Sectional Analysis of Abstinence Rates

Table 3 shows the percent abstinent for each treatment group at each scheduled visit, comparing continuous and point prevalence abstinence. The HCP group had higher abstinence rates than did the OTC group at all time points for both abstinence criteria. Rates of continuous abstinence were also significantly higher in the HCP group than in the OTC group at weeks 2, 6, and 26. Continuous abstinence rates were 13.46% vs 6.92% (P<.05), 10.77% vs 3.85% (P<.01) and, 4.62% vs 1.54% (P<.05) for the HCP and OTC groups respectively. However, the difference observed at week 52 was not statistically significant.

Seven-day point prevalence of abstinence was also significantly higher in the HCP group than the OTC group at each time point, ranging from 21.54% to 8.46% between weeks 2 and 52 in the HCP group and from 11.15% to 3.08% (respectively) in the OTC group (P<.001 at week 2, P<.01 at week 52). In general, the HCP intervention resulted in abstinence rates that were approximately 2 to 3 times higher than in the OTC group.

Longitudinal Analysis of Abstinence Rates

Table 4 shows 4 GEE models. Models 1 and 2 treat missed visits or missing CO verification as missing data, whereas models 3 and 4 treat such occasions as smoking. Models 1 and 3 consider the effects of treatment group, time, and their interaction term on point prevalence abstinence. Models 2 and 4 are pattern-mixture models. In pattern-mixture models, missing data patterns are entered as covariates to control for their nonrandom association with the outcome. The number of missed visits was used here.

All models show a consistently higher abstinence rate among HCP participants and a negative time-trend as well. Both of these results are consistent with cross-sectional results. No significant interaction effects were found in any model.

Note that self-efficacy, shown in Table 1, was significantly higher at baseline in the OTC group than in the HCP group. Because self-efficacy may be related to successful quitting, it was a potential confounder in the analysis. Moreover, although gender was balanced at baseline, differential attrition resulted in the OTC group having a significantly greater proportion of females than did the HCP group over time. Consequently, these variables

Table 4
7-Day Point Prevalence of Smoking Abstinence Quasi-Likelihood Estimates of Generalized Estimating Equations

	Model 1		Model 2		Model 3		Model 4	
Variable	Beta (SE)	Adjusted OR (95% CI)	Beta (SE)	Adjusted OR (95% CI)	Beta (SE)	Adjusted OR (95% CI)	Beta (SE)	Adjusted OR (95% CI)
Treatment Group (OTC=0; HCP=1)	1.066*** (0.268)	2.904*** (1.719, 4.909)	1.059*** (0.265)	2.883*** (1.714, 4.850)	0.818*** (0.233)	2.266*** (1.436, 3.579)	1.012*** (0.253)	2.751*** (1.675, 4.518)
Week(Wk)	0.001 (0.014)	1.001 (0.973, 1.029)	0.001 (0.012)	1.001 (0.978, 1.024)	-0.028*** (0.007)	0.972*** (0.959, 0.986)	-0.031*** (0.007)	0.969*** (0.956, 0.983)
Treatment x Wk Interaction	0.014 (0.016)	1.014 (0.983, 1.045)	0.014 (0.014)	1.014 (0.987, 1.041)	0.004 (0.008)	1.004 (0.988, 1.020)	0.003 (0.009)	1.003 (0.985, 1.021)
Gender (Female=0; Male=1)	-0.419 (0.218)	0.658 (0.429, 1.009)	-0.474* (0.228)	0.623* (0.398, 0.974)	-0.242 (0.213)	0.785 (0.517, 1.192)	-0.408 (0.224)	0.665 (0.428, 1.031)
Self-Efficacy - 24 hours	0.281** (0.107)	1.324** (1.073, 1.634)	0.288* (0.111)	1.334* (1.071, 1.655)	0.218* (0.108)	1.244* (1.007, 1.536)	0.251* (0.113)	1.285* (1.030, 1.603)
# Missed Visits	-- --	-- --	-0.453*** (0.096)	0.636*** (0.527, 0.768)	-- --	-- --	-0.855*** -(0.071)	0.425*** (0.370, 0.488)
# Observations	750		750		2049		2049	
Wald Chi-square	39.67***		66.02***		58.37***		194.95***	

Note.
*** P<0.05; ** P<0.01; ***P<0.001**
OTC = Over the Counter Setting; HCP = Health-Care Practitioner Setting
Numbers in parentheses are semirobust standard errors (SE).
Models 1 and 2 treat missed visits and missing CO verifications as missing data.
Models 3 and 4 treat missed visits and missing CO verifications as smoking.
Parameters reported are slope coefficients. Odds-ratio = exp (slope coefficient).
All sociodemographic and smoking characteristics with a reasonable potential for variation between groups (ie, P<.20) were assessed as potential confounders. None were found to be so, and so are not included in final models.

were included as potential confounders. The distributions of both variables were such that the positive effect of the HCP intervention on quitting would be attenuated. Indeed, the treatment effect is 10-20% greater than found in models where self-efficacy and gender were not included (results not shown here).

Participants who missed more clinic visits were more likely to be smoking at those visits where they were actually observed. A missing at random assumption is therefore untenable, making the pattern-mixture models (models 2 and 4) preferable to models 1 and 3. Because missed visits are treated as smoking in model 4, there is a high correlation between number of missed visits and smoking status, resulting in a stronger coefficient for number of missed visits in model 4 compared to model 2. However, the fact that number of missed visits is significant in both models shows that this result is not artifactual. In both sets of models, the pattern-mixture model suggests a stronger treatment-group difference. However, under all 4 models the probability of abstinence in HCP participants is consistently higher than that of OTC participants, indicating that the relationship is stable in the face of different treatments of missing data. In these models, the odds ratio for 7-day point prevalence abstinence among HCP relative to OTC participants ranges from 2.27 to 2.90.

DISCUSSION

The present study was designed to assess whether the use of the nicotine

inhaler for smoking cessation in an OTC setting would result in comparable abstinence rates when the inhaler is used in conjunction with health-care-provider support. This study found that at most follow-up visits the abstinence rates for the health-care-provider condition were significantly higher, and this outcome was fairly consistent when either strict (continuous abstinence) or more lax (point prevalence) criteria were used. Similarly, the differences between treatment conditions remained when intent to treat (all participants) and medication purchase conditions were compared. In fact, when only those who chose to purchase inhalers were included in the analysis, the difference in abstinence rates between the 2 treatments increased (results not shown here).

An important outcome of the present study is the very low abstinence level in both treatment conditions, but especially in the OTC condition. In the most stringent analysis of continuous abstinence in the intent-to-treat group, the abstinence rates in the OTC group were less than 1% at the end of 1 year. Point prevalence abstinence rates in that same group were not much higher, a little over 3%. One argument that could be made for why our quit rates were so low is that many of the participants who were lost to follow-up may have actually been abstinent. Because we assumed in the cross-sectional analyses that missing subjects were smokers, our estimates are very likely to be biased low. Unfortunately, we cannot determine the extent of any such bias precisely because those subjects were lost to follow-up. Like most other studies that have followed FDA guidelines for smoking cessation clinical trials, ours did not include the kinds of tracking systems that would have been necessary to assess that possibility. However, we did call every subject at or around week 52 who was eligible to be called (ie, had not withdrawn their consent), and we were able to contact a total of 258 individuals. Of these individuals, 132 were from the OTC group, and 126 were from the HCP group, so both groups were equally represented. Their self-reported continuous abstinence rates at that point were still only 1.5% in the OTC group vs 4.6% in the HCP group.

The low abstinence rates found in this study may have been due to several reasons. First, the screening process was not as stringent or lengthy as in many of the pharmacotherapy studies designed to be reviewed by the FDA because the nicotine inhaler is a very safe medication. Thus, the study may have included many smokers who were not very motivated to quit smoking. In order to balance collecting information that could be useful for additional analyses with the need to minimize time spent in data collection, such that that data collection could become a de facto treatment itself (particularly in the OTC condition), participants' readiness to quit was not assessed. Rather, we focused our attention in this study on treatment outcomes, with the understanding that future studies would be needed to tease out additional factors affecting treatment outcome. Second, unlike many clinical trials, this study had relatively few follow-up visits. The most recent PHS clinical guidelines[3] for tobacco cessation demonstrated a positive association between number of visits and treatment outcome. Because we provided few follow-up visits, the relative lack of contact may have resulted in lower abstinence rates. Conducting controlled studies that evaluate the switch of a smoking cessation medication from prescription to OTC is complicated by the need to balance data collection and tracking with the goal of being as lifelike as possible. For example, if an NRT OTC switch study includes 6 weekly follow-up visits post-quit day, those visits are, in effect, treatments that will by themselves increase rates of abstinence across conditions and thereby confound the effect of the medication alone.

Improper nicotine inhaler use may also have contributed to the overall low abstinence rates found in this study. The nicotine inhaler has a more difficult draw compared to a cigarette, resulting in more work in order to get sufficient quantities of nicotine to prevent withdrawal.[18] Our experience with nicotine inhaler is that adherence to the recommended dosing regimen is uncommon. In fact, the inhaler use patterns observed in the present study suggest that adherence was not sufficient. It would appear that either the product design needs to change so that more nicotine is available (though this is a double-edged sword because that would also likely increase abuse liability), or consumer behavior on nicotine inhaler use (ie, puffing topography) needs

to be altered. Because the efficacy of the inhaler is dependent on how it is used and because it is clear that many users do not puff on the inhaler often enough to get the nicotine needed to suppress withdrawal, additional proactive health education is needed to optimize the correct use of the nicotine inhaler. Clearly there are limitations to the present study, in addition to those mentioned above. No placebo group was used in this study because (a) we wanted to compare treatments in a head-to-head study that would have the greatest relevance to clinical practice, and (b) we believe that use of a placebo itself increases quit rates because it affects participants' motivations and expectations.[7] Furthermore, and because we wanted participants to pay a cost for the medication in order to better reflect a real OTC situation, we decided that it would not be ethical to charge participants for placebo inhalers. Certainly given the low abstinence rates found in this study, one cannot argue that the outcomes were artificially high because no placebo was used.

The outcomes of this study are in some respects different, and in other respects similar, to those of our earlier study with a similar design that assessed the efficacy of OTC nicotine patch.[5] In that study, we found that there was no abstinence rate difference between the OTC and HCP conditions. However, like the present study, our patch OTC likewise found that abstinence rates in the OTC group were very low. The results of this study are not consistent with those of other studies that compared OTC NRT with prescription NRT,[4] in that this study found significantly higher quit rates in the prescription group than in the OTC group. The present study was the only one that assessed OTC inhaler, so it may be that this NRT medication more than others requires a significant behavioral support program for it to be efficacious.

One possible reason for why we found increased efficacy in the HCP condition in this study, and not the OTC patch study, is that our HCP treatment in the present study was much more consistently provided. A nurse practitioner with considerable prior experience providing smoking cessation treatment provided all of the HCP intervention in this study. It should be noted, however, that the intent of the HCP group was to test what is clearly an imperfect clinical intervention. Optimal HCP intervention was not provided in all cases in this trial, even though considerable clinical standardization was required. This suggests that HCPs in nonresearch settings where there is less standardization are even less likely to provide recommended help to smokers. Yet, our finding of increased quit rates even with 46% adherence by the HCP speaks to the value of this type of intervention if we can increase the role of the HCPs. In our OTC patch study, there were multiple HCPs (including physicians) who provided brief counseling during the 2 counseling visits. Increased variability in HCP counseling effort in our OTC patch study may have resulted in inadequate intervention and hence comparable abstinence rates between the 2 treatment conditions. Although the present study may not be generalizable to some real-world environments, our results demonstrate clearly that HCP intervention in addition to use of the nicotine inhaler will increase quit rates over OTC use of inhaler alone.

Several conclusions can be drawn from the results of the present study. First, health-care providers make a difference. It is not enough for smokers to simply purchase nicotine inhalers and then hope for the best. Health-care providers remain a critical part of the smoking cessation process, even in an environment of easy access to OTC smoking cessation medications.

Second, OTC use of the nicotine inhaler does not result in an adequate abstinence rate when no adjunctive behavioral support is provided. It may be that if an effective behavioral support package were included, the abstinence rates in the OTC study may have been higher. However, actual use of behavioral support materials for smoking cessation is, in our experience, more the exception than the rule even when it is a free service (eg, a toll-free number). Additional research on behavioral support materials and methods that have the potential to increase abstinence rates when OTC medications are purchased is needed. Third, medication adherence was inadequate. The nicotine inhaler delivers very little nicotine on a puff-per-puff basis,[18] and many smokers may have become frustrated because they could not get enough nicotine to suppress withdrawal symptoms.

Strategies that will increase adherence are needed.

Do the results of this study suggest that the nicotine inhaler should not be approved for OTC use because it is ineffective? Not necessarily. There is ample evidence that when the nicotine inhalers are used appropriately, abstinence rates are at least comparable to other forms of NRT.[3] Effective adjunctive support needs to be provided with the OTC inhalers so that smokers have a reasonable chance of quitting with this medication, rather than filling their medicine cabinet with more medications that collect dust as they continue to smoke.

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