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Efficacy of the nicotine inhaler in smoking reduction: A double-blind, randomized trial

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Many smokers are not ready to quit but are interested in changing their smoking behavior, particularly if such a change is associated with a reduction in health risk. The present study evaluated the efficacy of the nicotine inhaler in reducing smoking. Exploratory studies assessed whether reduction in smoking was associated with reduction in markers of disease risk. A total of 429 healthy smokers (smoking at least 20 cigarettes/day) were randomly assigned to either nicotine-containing or placebo inhalers, which subjects were allowed to use ad libitum for up to 1 year. The nicotine inhaler was significantly superior to placebo in achieving reduction in daily cigarette consumption by at least 50% after 4 months, compared with baseline (18% vs. 8%, $p=.004$). Active treatment promoted smoking cessation: 8% of subjects in the nicotine group and 1% in the placebo group were abstinent at month 15. Throughout the study, smoking reduction, per se, independent of treatment group, was associated with a statistically significant decrease in exhaled carbon monoxide and serum cotinine and thiocyanate. Smoking reduction also improved established risk markers for cardiovascular disease over 4 months. The incidence of adverse events did not differ significantly between the active and placebo groups. The most common treatment-related adverse events were throat irritation and cough. In conclusion, the nicotine inhaler can help smokers who are unable or unwilling to quit to reduce daily cigarette consumption, which may be a health benefit on its own and may further promote quitting.

Introduction

Cigarette smoking is the most common preventable cause of morbidity and mortality in the developed world (U.S. Department of Health and Human Services [USDHHS], 1984). The best means to prevent the health burden caused by smoking is to prevent smoking initiation. Although recent public health campaigns have had some impact on smoking initiation rates (Johnston, O'Malley, & Bachman, 2003), many young people continue to start smoking. The next best means, for individuals who smoke, is smoking cessation, the health benefits of which are well established (USDHHS, 1989, 1990). Current interventions, however, can help only a minority of smokers to quit. Encouraging abrupt cessation as the only option currently motivates only a small proportion of smokers and does not help those who have tried to quit and failed, those who do not want to quit, or those who are not ready to give up smoking completely.

Attention is therefore turning to the need for interventions aimed at treatment-resistant smokers (Bolliger et al., 2000; Fagerström, 1999; Jimenez-Ruiz, Kunze, & Fagerström, 1998; Shiffman, Mason, & Henningfield, 1998), and additional strategies to reduce the health consequences caused by smoking have been suggested (Institute of Medicine, 2001). Among these strategies is reduction of the amount

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smoked for individuals who are unable or unwilling to quit. However, simply trying to reduce the number of cigarettes smoked is unlikely to succeed because most smokers are addicted to nicotine and regulate their smoking behavior in order to maintain nicotine intake (Hofer, Nil, & Battig, 1991; Petitti & Friedman, 1983; Russell, Sutton, Feyerabend, & Saloojee, 1980; Scherer, 1999; Sutton, Feyerabend, Cole, & Russell, 1978; Sutton, Russell, Iyer, Feyerabend, & Saloojee, 1982).

Supplying nicotine from an alternative source could help smokers to reduce their cigarette consumption. The nicotine inhaler relieves tobacco withdrawal symptoms (Lunell, Molander, Leischow, & Fagerström, 1995) and can effectively aid smoking cessation (Hjalmarson, Nilsson, Sjostrom, & Wiklund, 1997; Leischow et al., 1996; Leischow, Ranger-Moore, Muramoto, & Matthews, 2004; Schneider, Olmstead, Franzon, & Lunell, 2001; Tonneson, Norregaard, Mikkelsen, Jorgensen, & Nilsson, 1993), and one study has shown that the inhaler can aid smoking reduction (Bolliger et al., 2000). This investigation was therefore designed to evaluate the nicotine inhaler as a smoking reduction aid using well-established biomarkers associated with smoking-induced disease as secondary outcomes. Other goals of the present study were to determine the effect of the nicotine inhaler used for smoking reduction on quit attempts and motivation to quit in a group of smokers who were unwilling to make a current quit attempt.

Method

Study design and patients

This double-blind, parallel group, randomized, multicenter study used newspaper advertisements to enroll healthy adult smokers who wanted to reduce smoking. The study was performed at three U.S. study sites (Tucson, Arizona; Morgantown, West Virginia; and Omaha, Nebraska) from August 1999 through April 2001. It was conducted in accordance with the ethical principles in the Declaration of Helsinki and subsequent revisions. The study protocol was approved by an institutional review board at each site, and written informed consent was obtained from all patients before randomization.

To be eligible, subjects had to be 18 years or older, smoke at least 20 cigarettes/day, have smoked for at least 3 years, have an exhaled carbon monoxide [CO] level of at least 15 ppm (parts per million) after 15 smoke-free minutes, have failed at least one serious quit attempt within the previous 2 years, and want to reduce their cigarette consumption. Subjects who planned to quit smoking within the next 4 weeks or who scored 9 or 10 on the Contemplation Ladder were excluded (Biener & Abrams, 1991). Other exclusion criteria were current use of nicotine replacement or any other behavioral or pharmacological smoking cessation or reduction program, use of other nicotine-containing tobacco products, unstable angina pectoris or myocardial infarction within the preceding 3 months, pregnancy or lactation, being under psychiatric care or taking psychiatric medication, and alcohol or drug abuse that could interfere with the trial. There were nine clinic visits over 15 months (baseline; weeks 2, 6, and 10; and months 4, 6, 9, 12, and 16).

Medications

Subjects were randomized to receive either 10-mg nicotine inhaler (Nicotrol/Nicorette, Pfizer Consumer Healthcare) or a matched placebo inhaler identical to the active treatment with the nicotine excluded. Both inhalers included 1 mg of menthol. The inhalers could be used ad libitum, with a recommended dose of 6–12 cartridges per day, for up to 12 months. Subjects received enough inhalers to cover the maximum dose for the first 2 weeks, and thereafter the number of inhalers dispensed was individualized to each participant. Participants could collect more inhalers between visits if needed. Subjects were instructed to reduce their smoking as much as possible and were provided with information on possible ways to do so. No, or very little, additional supportive interventions were provided. Smoking cessation was recommended from month 6 as the long-term goal but was not mandatory.

Outcome measures

The primary outcome was self-reported reduction in the number of cigarettes smoked per day by at least 50% (including quitters) compared with baseline, from week 6 to month 4. Smoking reduction was verified by a decrease in expired CO of at least 1 ppm compared with baseline. Secondary outcomes were the effect of smoking reduction on smoking cessation (point-prevalence abstinence for at least 7 days, verified by CO less than 10 ppm), intention to quit smoking, smoking-related symptoms, quality of life, and risk markers for cardiovascular disease. We conducted a post-hoc analysis comparing biological measures in reducers, excluding those who quit.

Assessments

Nine clinic visits were scheduled; eight between baseline and the end of the 12-month treatment period, and one follow-up visit at 15 months. At baseline, medical and smoking histories were obtained, vital signs noted, and exhaled CO

Table 1. Baseline characteristics of subjects enrolled.

Characteristic	Nicotine inhaler (n=215)	Placebo inhaler (n=214)
Age, years	45.9 (12.3)	44.8 (12.1)
Male/female	88/127	104/110
Body mass index	27.8 (5.9)	27.2 (5.4)
Age when started smoking, years	17.1 (3.9)	16.8 (3.5)
Number of cigarettes smoked per day	29.3 (10.1)	30.4 (9.9)
Expired carbon monoxide, ppm	29.7 (10.7)	29.5 (9.0)
Nicotine dependence, FTND score	6.5 (2.0)	6.6 (1.9)

Note. Values are means with standard deviations, except for male/female. FTND, Fagerström Test for Nicotine Dependence.

measured. At each visit, self-reported smoking status was recorded and then verified using expired CO measurements. Subjects reported their inhaler use and completed questionnaires on intention to quit.

Blood samples were taken at 4, 12, and 15 months for determination of plasma cotinine and thiocyanate levels. Tobacco dependence was assessed using the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Quality of life (using a revised RAND 36-item health survey; Hays, Sherbourne, & Mazel, 1993) and smoking-related symptoms (cough, phlegm, shortness of breath, and senses of smell and taste) were assessed at baseline and after 4, 12, and 15 months. Blood samples also were taken to analyze established biomarkers of cardiac disease: White blood cells, cholesterol (high-density lipoprotein, low-density lipoprotein), fibrinogen, and C-reactive protein. Adverse events were assessed at each visit using open-ended questions.

Data analyses

The primary analysis was performed on an intention-to-treat basis and included all subjects who were randomized and received medication. Subjects who withdrew early or were lost to follow-up were classified as failures. All statistical tests were two-sided and at the 5% significance level. Fisher's exact test was used to analyze binary variables, and continuous variables were analyzed using the Kruskal–Wallis test. The Wilcoxon signed rank-sum test was used to investigate changes from baseline for continuous variables.

The sample size was based on previous results from smoking reduction studies; we estimated that at 4 months, 20% of the active group and 10% of the placebo group would have reduced their smoking by at least 50% compared with baseline. Using this assumption, we needed 197 subjects in each group to have a power of 80% to detect a difference at a significance level of .05.

Results

Study population

A total of 2,306 subjects were screened, of whom 429 met the criteria for inclusion and were enrolled. Of those subjects, 215 received the 10-mg nicotine inhaler and 214 the placebo inhaler. Baseline characteristics for both groups are shown in Table 1. A total of 154 subjects (89 active, 65 placebo) completed the 15-month study. Thus, 275 subjects dropped out during the study (126 active, 149 placebo). The most common reasons were "not willing to participate" (n=99), "lost to follow-up" (n=40), and "unable to reduce smoking" (n=28). A total of 100 subjects dropped out because of other reasons not further specified.

Treatment use

Compliance with treatment among continuing participants was good. At 2 weeks, daily inhaler use was reported by 73% of the active group vs. 68% of the placebo group; at 4 months, these values were 48% vs. 38%, respectively. The mean number of inhaler cartridges used per day at 4 months was 6.4 (SD=2.7) in both treatment groups (daily users). Inhaler use throughout the study is summarized in Table 2.

Table 2. Number of inhalers used by daily users.

	Nicotine inhaler (n=215)		Placebo inhaler (n=214)	
Time point	Sample size	Number of inhalers/day[a]	Sample size	Number of inhalers/day[a]
2 weeks	158	5.7 (2.6); 1–12	145	6.9 (3.0); 1–16
6 weeks	136	6.6 (2.8); 1–17	116	7.4 (2.9); 1–16
4 months	103	6.4 (2.7); 2–12	84	6.4 (2.8); 1–12
6 months	73	6.0 (2.8); 1–12	58	6.0 (3.1); 1–12
9 months	48	6.4 (3.2); 1–14	36	5.9 (3.1); 1–12
12 months	43	5.8 (3.1); 1–12	23	6.6 (3.6); 1–12

Note. [a]Values are means with standard deviations, followed by ranges.

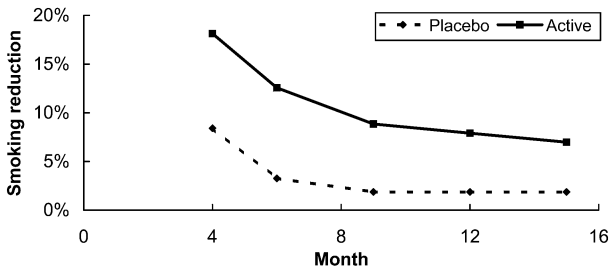

Figure 1. Sustained smoking reduction by at least 50% versus baseline from week 6. Fisher's exact test, $p<.05$ at all time points.

Smoking reduction

The nicotine inhaler was significantly superior to placebo in achieving smoking reduction. After 4 months, 18% of subjects in the active group had reduced their daily smoking by at least 50% from the baseline established at week 6, compared with 8% in the placebo group ($p=.004$). The nicotine inhaler also was superior to placebo in maintaining smoking reduction up to 12 and 15 months (Figure 1). The average number of cigarettes smoked per day decreased by 74% among the 39 subjects who reduced 50% using the inhaler (from 29.1 ± 9.7 to 7.6 ± 8.6, $p<.001$). Although significantly fewer subjects reduced using placebo, the 18 subjects who did reduce by 50% reported a similar 74% reduction in cigarettes smoked per day (from 31.9 ± 14.1 to 8.1 ± 13.7, $p<.001$).

There was a trend for greater overall reduction in the number of cigarettes smoked in the group treated with the inhaler (Table 3). Statistical comparisons based on average cigarette consumption were not performed because there were differential dropouts and there was likely no reduction in this group (data not shown).

Smoking cessation

Smoking cessation rates (point prevalence) also were higher in the nicotine inhaler group than in the placebo group, 7.9% versus 2.3% ($p=.014$) at 12 months, and 7.9% versus 1.4% ($p=.002$) at 15 months (Figure 2).

Participation in the smoking reduction trial had a favorable effect on both intention to quit and attitude toward smoking cessation. At month 15, 17% of subjects in the nicotine inhaler group and 18% in the placebo group (excluding those who had already quit) expressed an intention to quit, compared with 1% and none, respectively, at week 2. In addition, 87% (254/293) of subjects at month 4, and 80% (128/161) of subjects at month 15, stated that they were more interested in quitting than before taking part in the study.

Table 3. Average cigarette consumption among subjects continuing in the trial by treatment group.

	Placebo group						Active group					
	Number of cigarettes/day			Cigarettes/day changes from baseline			Number of cigarettes/day			Cigarettes/day changes from baseline		
Visit	*n*	*M* (*SD*)	Range	*n*	*M* (*SD*)	Range	*n*	*M* (*SD*)	Range	*n*	*M* (*SD*)	Range
Baseline	214	30.4 (9.9)	20.0 to 60.0	214	0.0 (0.0)	0.0 to 0.0	215	29.3 (10.1)	20.0 to 60.0	215	0.0 (0.0)	0.0 to 0.0
2 weeks	185	19.4 (7.7)	5.0 to 45.0	185	−10.8 (7.6)	−51.0 to 2.0	200	17.3 (8.1)	0.0 to 53.0	200	−11.7 (8.4)	−55.0 to 5.0
6 weeks	154	17.0 (7.8)	0.0 to 40.0	154	−12.7 (9.1)	−51.0 to 10.0	177	15.2 (8.2)	0.0 to 47.0	177	−13.6 (8.7)	−50.0 to 0.0
10 weeks	148	16.7 (8.6)	0.0 to 45.0	148	−13.7 (9.7)	−58.0 to 2.0	163	14.9 (9.4)	0.0 to 50.0	163	−14.0 (8.6)	−50.0 to 5.0
4 months	139	16.3 (8.4)	0.0 to 40.0	139	−13.2 (9.6)	−58.0 to 5.0	154	14.4 (9.6)	0.0 to 50.0	154	−14.4 (8.8)	−50.0 to 9.0
6 months	106	16.6 (9.7)	0.0 to 40.0	106	−13.4 (11.2)	−59.0 to 10.0	129	13.7 (9.6)	0.0 to 40.0	129	−14.6 (8.6)	−50.0 to 10.0
9 months	81	18.7 (11.9)	0.0 to 50.0	81	−11.8 (11.7)	−55.0 to 18.0	105	13.8 (10.2)	0.0 to 40.0	105	−14.2 (8.9)	−50.0 to 0.0
12 months	76	17.4 (10.6)	0.0 to 40.0	76	−12.6 (10.2)	−55.0 to 10.0	96	13.3 (10.8)	0.0 to 40.0	96	−14.5 (10.2)	−50.0 to 4.0
24 months	66	17.7 (12.4)	0.0 to 60.0	66	−12.2 (10.7)	−55.0 to 20.0	89	13.1 (11.6)	0.0 to 40.0	89	−14.6 (10.2)	−50.0 to 0.0

Note. *M*, mean; *n*, sample size; *SD*, standard deviation.

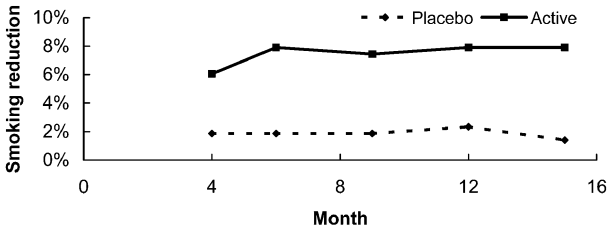

Figure 2. Point-prevalence abstinence, verified by expired CO level <10 ppm. Fisher's exact test, $p<.05$ at all time points.

Exploratory measures of the impact of smoking reduction

Although the number of study subjects was small, exploratory analyses were conducted to determine if smoking reduction per se was associated with changes in clinical features, measures of exposure, and markers of disease risk. We found no statistically significant differences between the treatment groups. However, significant changes were observed for those subjects who achieved reduction across both treatment groups.

Smoking-related symptoms and quality of life. For all subjects, changes in smoking-related symptoms correlated with the extent to which CO was reduced. The greatest improvements in cough, phlegm, shortness of breath, and senses of smell and taste were observed in subjects who had succeeded in reducing their mean expired CO by at least 50% compared with baseline.

With respect to quality of life, at 4 and 15 months, respectively, statistically significant improvements in self-control ($p<.001$), which is a specific item on the smoking scale, were noted for subjects who had reduced their mean cigarette consumption by at least 50%. We found no statistically significant changes in any other quality-of-life items.

The 20 subjects who had successfully quit smoking at month 15 had gained a mean of 5.0 kg compared with the not significant weight change in subjects who had not quit smoking ($p<.001$).

Markers of exposure. The correlation between decrease in expired CO levels and magnitude of reduced smoking from baseline to month 15 was highly significant (Table 4). In the two treatment groups combined, plasma cotinine and thiocyanate levels were statistically significantly more reduced in subjects who reduced their smoking by at least 50% compared with subjects who did not reduce smoking to that extent (Table 5). Interestingly, for the group that did not achieve the 50% reduction goal, we found trends toward reduction in biomarkers that were of greater magnitude and more likely significant for both cotinine ($p=.002$) and thiocyanate ($p=.009$) in the active group compared with the placebo group (nicotine, $p=.035$; thiocyanate, $p=.146$). This finding suggests an effect of the active treatment even in those who did not meet the criterion of 50% reduction.

Changes in cardiovascular risk factors following smoking reduction. At 4 months, for all individuals who achieved the smoking reduction criterion of 50% reduction, including point-prevalence quitters, we found a statistically significant increase in high-density lipoprotein ($p=.003$), as well as decreases in white blood cells ($p=.03$), low-density lipoprotein (*ns*), fibrinogen (*ns*), and C-reactive protein ($p=.04$); see Table 6. The present study was designed primarily as a smoking reduction trial. Cessation, however, is clearly the best option to minimize health risks. All participating subjects were screened, and no individuals interested in making a quit attempt within 30 days were recruited. Nevertheless, some subjects, after a period of reduction, were interested in making quit attempts, and they were encouraged to do so. The study was neither designed nor adequately powered to separately evaluate those who partially reduced from those who reduced completely (i.e., who quit).

The intention-to-treat primary analysis was designed to compare placebo with active inhaler, with a primary outcome of smoking reduction, which did show a significant difference. Also of interest, however, is a determination of whether those who quit accounted for the improvements in markers of health risks observed. Values for those who were reducers and those who were point-prevalent quitters at 4 months are presented in Table 6. As can be expected, the subgroup analyses lost sufficient

Table 4. Changes in expired carbon monoxide levels (ppm) at 15 months compared with baseline.

Mean cigarette reduction, week 6 to month 15	Baseline		Change from baseline		
	Sample size	*M* (*SD*)	*M* (*SD*)	95% Confidence interval	Range
>75%	21	31.4 (15.2)	−25.2 (15.6)	(−32.3, −18.1)	−63.0 to −3.0
50% to ⩽75%	39	25.7 (9.2)	−8.3 (9.4)	(−11.3, −5.2)	−30.0 to 11.0
25% to <50%	56	30.9 (9.8)	−8.0 (12.0)	(−11.2, −4.7)	−45.0 to 23.0
<25%	18	31.4 (8.5)	−4.6 (5.8)	(−7.5, −1.7)	14.0 to 9.0

Note. *M*, mean; *SD*, standard deviation.

Table 5. Changes in plasma cotinine and thiocyanate levels in reducers and nonreducers at 4 months compared with baseline.

			Cotinine (ng/ml)				Thiocyanate (ng/ml)			
		Sample size	Baseline[a]	Change from baseline[a]	Within-group *p* value	Between-group *p* value*	Baseline[a]	Change from baseline[a]	Within-group *p* value	Between-group *p* value*
Reduced ⩾50%	Active	38	266.1 (123.8)	−59.9 (115.7)	.003	0.013	8.78 (2.94)	−1.72 (2.83)	<.001	.004
	Placebo	17	332.5 (194.4)	−97.9 (123.3)	.005		9.39 (3.47)	−1.59 (2.62)	.024	
	Total	55	286.6 (150.5)	−71.6 (118.3)	<.001		8.97 (3.09)	−1.68 (2.74)	<.001	
Reduced <50%	Active	106	275.5 (100.0)	−25.3 (80.5)	.002		9.97 (2.58)	−0.56 (2.17)	.009	
	Placebo	114	293.0 (104.9)	−18.1 (90.8)	.035		9.59 (2.33)	−0.27 (1.96)	.146	
	Total	220	284.6 (102.7)	−21.58 (85.87)	<.001		9.77 (2.45)	−0.41 (2.06)	.008	

Note. [a]Values are means with standard deviations. *The *p* value for the difference between reduced (total) and not reduced (total).

sample size to achieve statistical significance for most parameters. Nevertheless, trends and in some cases significant improvements in the parameters measured were observed among those who reduced but did not quit as well as in those who achieved complete abstinence.

Safety

Adverse events were reported by 159 subjects in the nicotine inhaler group and 147 subjects in the placebo group. Most adverse events were mild or moderate and were unrelated to study treatment. As in previously published studies (Hjalmarson et al., 1997; Leischow et al., 1996, 2004; Schneider et al., 2001; Tonneson et al., 1993), the incidence of adverse events that were possibly treatment related (nausea or vomiting) was low in the active (n=11) and placebo (n=5) treatment groups. A total of 28 serious adverse events were reported, none of which was related to study treatment. The most common treatment-related adverse events were throat irritation (15 in the active group vs. 6 in the placebo group; *ns*) and cough (12 in the active group vs. 5 in the placebo group; *ns*). A total of 9 subjects in the active group reported 15 serious adverse events compared with 13 reports by 11 subjects in the placebo group. None of these events was assessed as being related to study medication.

Discussion

The vast majority of smokers are not ready to make an abrupt quit attempt and may benefit from a smoking reduction strategy (Boyle, Gandini, & Robertson, 2000). The present study showed that use of a nicotine inhaler led to a sustained reduction in daily cigarette consumption for 15 months and promoted smoking cessation, although no subjects expressed an intention to quit on enrollment. Although we found no statistical differences between treatment groups, perhaps because the number of subjects was small, reduced smoking across the groups was associated with reductions in markers of exposure for tobacco smoke, with a strong correlation between extent of smoking reduction and levels of expired CO.

The present study used partial nicotine replacement to avoid the problem of compensatory smoking. The lack of change in levels of cotinine, a major metabolite of nicotine, in both reducers and nonreducers over 4 months suggests that nicotine intake was maintained in both groups. This contrasts with other measures of cigarette exposure, with reducers demonstrating a reduction in exhaled CO, a cigarette-derived toxin. Another, not entirely tobacco-specific toxin, thiocyanate, also was assessed

Table 6. Effect of reducing smoking by at least 50% on risk factors for cardiovascular disease.

Parameter	Abstinent at month 4	Sample size[a]	Baseline	Change from baseline to month 4				
			M (*SD*)	*M* (*SD*)	95% Confidence interval	Median	Range	*p* value[b]
White blood cells, $\times 10^9$/l	All	54	7.78 (1.85)	−0.34 (1.42)	(−0.73, 0.04)	−0.45	−3.0 to 4.6	.03
	No	43	7.78 (1.87)	−0.23 (1.37)	(−0.65, 0.20)	−0.40	−2.9 to 4.6	.17
	Yes	11	7.75 (1.86)	−0.81 (1.58)	(−1.87, 0.25)	−1.10	−3.0 to 3.0	.07
High–density lipoprotein, mg/dl	All	56	43.8 (14.5)	2.11 (5.20)	(0.71, 3.50)	3.00	−12.0 to 10.0	.003
	No	44	44.8 (15.2)	1.73 (5.36)	(0.10, 3.36)	3.00	−12.0 to 10.0	.03
	Yes	12	40.2 (11.3)	3.50 (4.52)	(0.63, 6.37)	4.00	−6.0 to 10.0	.04
Low–density lipoprotein, mg/dl	All	55	133.6 (41.3)	−5.76 (32.3)	(−14.5, 2.97)	−5.00	−164.0 to 60.0	.23
	No	43	135.4 (42.7)	−5.09 (33.1)	(−15.3, 5.10)	0.00	−164.0 to 48.0	.53
	Yes	12	126.8 (36.9)	−8.17 (30.5)	(−27.5, 11.2)	−120.0	−63.0 to 60.0	.18
Fibrinogen, mg/dl	All	52	319.1 (76.3)	−18.6 (71.0)	(−38.4, 1.12)	−4.00	−191.0 to 130.0	.15
	No	42	314.1 (79.7)	−18.9 (75.9)	(−42.5, 4.76)	−1.50	−191.0 to 130.0	.23
	Yes	10	340.5 (58.2)	−17.6 (48.1)	(−52.0, 16.8)	−6.50	−102.0 to 48.0	.38
C4–reactive protein, mg/dl	All	56	0.53 (0.43)	−0.09 (0.39)	(−0.20, 0.01)	0.00	−2.66 to 0.32	.04
	No	44	0.54 (0.47)	−0.09 (0.42)	(−0.22, 0.03)	0.00	−2.66 to 0.17	.07
	Yes	12	0.52 (0.22)	−0.09 (0.25)	(−0.25, 0.08)	0.00	−0.64 to 0.32	.31

Note. M, mean; *SD*, standard deviation. [a]Data missing for some subjects. [b]Wilcoxon signed rank-sum test.

and declined more markedly in reducers than in nonreducers. These observations support the concept that partial nicotine replacement using the nicotine inhaler was associated with a true reduction in smoking. The efficacy of the nicotine inhaler as an aid for smoking reduction confirms and extends the results reported by Bollinger et al. (2000). How the nicotine inhaler would compare with other forms of nicotine replacement is undetermined.

The present study also indicated the benefits of smoking reduction on risk markers for cardiovascular disease. Established cardiovascular risk markers were generally improved in subjects who reduced their cigarette smoking by 50% compared with baseline. Improvements in cardiovascular risk markers also were noted in earlier studies in which subjects used either the nicotine inhaler (Bolliger et al., 2002) or the nicotine nasal spray (Eliasson, Hjalmarson, Kruse, Landfeldt, & Westin, 2001) to reduce smoking. The present study was not powered to compare active inhaler vs. placebo based on improvement in biomarkers but rather on achieving reduction. In this context, the study demonstrated a statistically significant effect of active inhaler in achieving reduction, the primary hypothesis being tested. This was true even though the placebo may have had "activity" because of the flavorings or the way in which it was used. The present study did not demonstrate a treatment effect on the measures of risk. However, as the issue of whether reduction itself is associated with health benefits, the improvement of biomarkers of risk among all of the reducers is of interest. In this context, reduction per se was associated with reduction in biomarkers of risk. The present study did not demonstrate the ideal way to achieve reduction to reduce risk of disease. The nicotine inhaler, however, may offer advantages, compared with other forms of nicotine replacement, because it is available on an as-needed basis and mimics some of the oral manipulations of a cigarette.

The dropout rate in the present study was 64%. Problems with dropouts are frequent and recurrent problems in studies on smoking cessation and smoking reduction. In the present trial, subjects were given relatively little behavioral counseling, which may have contributed to the dropout rate. The majority of subjects, moreover, dropped out because of lack of continuing interest or for unspecified reasons. Whether greater overall reduction could have been achieved with a more aggressive behavioral program remains to be determined.

The most rigorous method to test a treatment versus a placebo is generally regarded as an intention-to-treat analysis, and the most rigorous method to handle dropouts has been to regard all nonattendees as treatment failures. This latter approach is

based on the observation that the most common reason to drop from a smoking intervention trial is relapse to smoking at baseline levels. With this approach, dropouts generally increase the likelihood of a Type II error in the intention-to-treat analysis, that is, wrongly concluding that the intervention has no effect. Because we observed an effect of the active inhaler in facilitating reduction, the use of this approach strengthens the conclusions we made regarding the efficacy of the inhaler. It is possible, of course, that many of the dropouts also achieved reduction. Such an event, which seems unlikely, would confound the interpretation. Of interest, the average cigarette consumption in the treatment group dropped more than it did in the placebo group. Should the dropouts, which were more numerous in the placebo group, have not reduced, as we believe likely, this would further magnify this trend. Of course, a large reduction in smoking in the dropouts treated with placebo would have the opposite effect. It should be recognized, however, that the conclusions made in the present study are based on the data available.

Concomitant use of nicotine inhaler and cigarette smoking was well tolerated, with no unexpected or serious treatment-related adverse events. The incidence of symptoms of possible nicotine overdose was similar in the active and placebo groups. These findings reflect other clinical (Bolliger et al., 2000; Murray et al., 1996; Wennike, Danielsson, Landfeldt, Westin, & Tonnesen, 2003) and experimental (Stahl, Wohlfart, & Pahlm, 2001) studies in which nicotine medications were used while smoking, and a recent review that concluded the safety of concurrent use of nicotine replacement therapy and cigarette smoking (Fagerström & Hughes, 2002).

Because the majority of smokers, at any time point, are not ready to quit smoking (Etter, Perneger, & Ronchi, 1997), cessation is not an option. Reduction in the amount smoked, however, is not simple. Compensatory smoking is well established both for smokers under experimental conditions and for smokers who switch to low-tar, low-nicotine cigarettes (Benowitz et al., 1983; Kozlowski et al., 1998). The latter compensate by smoking more, particularly by smoking more intensely. Compensatory smoking maintains toxin intake, negating the anticipated reduction in toxin exposure (Scherer, 1999). Thus use of these tobacco products is not associated with any demonstrable health benefits (Kozlowski, 2002). An alternative strategy to reduce the health risk of smokers is to replace the nicotine from cigarettes with nicotine derived from other sources (Bolliger et al., 2000; Eliasson et al., 2001; Etter, Laszlo, Zellweger, Perrot, & Perneger, 2002; Fagerström & Hughes, 2002; Fagerström & Ramstrom, 1998; Hughes, Cummings, & Hyland, 1999; Jimenez-Ruiz et al., 1998; Jimenez-Ruiz et al., 2002; Rennard et al., 2002; Wennike et al., 2003). In one study, reduced smoking was associated with improvement in lower respiratory tract inflammation (Rennard et al., 1990). In another study, reduced carboxyhemoglobin levels and improved myocardial function were observed in a group of patients with known coronary artery disease (Mahmarian, Moye, & Nasser, 1997).

Smoking reduction, however, raises a number of important issues. Cessation undoubtedly reduces health risks more than reduction, and a primary concern regarding smoking reduction is that it may lead to smoker complacency and reduced attempts to quit. Interestingly, the opposite may be true, and recent investigations suggest that reduction may be a bridge to cessation for a number of smokers (Carpenter, Hughes, Solomon, & Callas, 2004; Etter et al., 2002; Hughes, 2000; Wennike et al., 2003). Our study also confirmed that the reduction concept facilitates quitting despite the study population (i.e., smokers not willing to currently quit). Several smokers significantly reduced their cigarette use for an extended time period and then gradually returned to customary smoking. For them, a reduction-only design may have represented an opportunity lost. Although the currently preferred strategy is abrupt quitting, cigarette-fading strategies have also demonstrated efficacy (Cinciripini et al., 1995), and the smoking reduction observed in our trial may have a similar beneficial effect. The increased "self-control" observed after reduction may have empowered some smokers to make a subsequent quit attempt. Smoking reduction may have other adverse public health effects including diversion of resources from other tobacco control programs as well as potentially eroding the public attitude limiting smoking behavior. Although such considerations are beyond the investigational scope of this paper, they should be considered in the implementation of any harm reduction strategy (Hatsukami et al., 2002).

In conclusion, the present study evaluated the use of the nicotine inhaler to facilitate smoking reduction. Partial nicotine replacement was associated with effective reduction in smoking. This was associated with improvements in risk markers for cardiovascular disease, supporting the concept that a smoking reduction approach may have health benefits. Smoking reduction facilitated rather than compromised subsequent quitting. The present study, therefore, supports the use of partial nicotine replacement with the nicotine inhaler as one component of a comprehensive tobacco control program.

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