Safety of Nicotine Polacrilex Gum Used by 3,094 Participants in the Lung Health Study*

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Study objective: **To assess cardiovascular conditions and other side effects associated with the use of nicotine polacrilex (NP), 2 mg.**
Design: **A multicentered randomized control trial of early intervention for the prevention of COPD.**
Setting: **Ten university medical centers in the United States and Canada.**
Participants: **Adult smoking volunteers with evidence of early COPD; 3,923 in intervention and 1,964 controls.**
Intervention: **Smoking cessation program, including NP.**
Measurements: **Data on hospitalizations were collected annually. Data on reported NP side effects were collected at 4-month intervals for intervention participants.**
Results: **The rates of hospitalization for cardiovascular conditions and cardiovascular deaths during the 5 years of the study were not related to use of NP, to dose of NP, or to concomitant use of NP and cigarettes. About 25% of NP users reported at least one side effect, but most were very minor and transient. Side effects associated with discontinuance of NP in 5% or more of users included headache, indigestion, mouth irritation, mouth ulcers, and nausea. There was no evidence that concomitant use of NP and cigarettes was associated with elevated rates of reported side effects. Participants in the smoking cessation intervention who received intensive levels of instruction and monitoring of NP use (initially at 12 meetings during 3 months) appeared to report significantly lower rates of side effects (dizziness, headache, and throat irritation) than control participants, presumed to have less instruction and monitoring.**
Conclusions: **NP, as used in the Lung Health Study, appears to be safe and unrelated to any cardiovascular illnesses or other serious side effects.**
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CI=confidence interval; CO=carbon monoxide; NHLBI=National Heart, Lung, and Blood Institute; NP=nicotine polacrilex

Key words: cardiovascular illness; clinical trial; nicotine gum; side effects; smoking cessation

Nicotine polacrilex (Nicorette) became available in the United States as a prescription drug 3 years before the Lung Health Study began in 1987. It had been clearly demonstrated to improve smoking cessation rates when used appropriately.[1] In the prescribing information supplied for the product, two studies reporting side effects were quoted.[2,3] These two studies exposed a total of 152 participants to NP, and both used placebo control groups in a double-blind procedure.

Side effects attributed to NP in studies have been predominantly minor (jaw muscle ache, air swallowing, denture adhesion, throat irritation, hiccups, stomachache).[4] The study duration after which side effects data are reported is typically only a few months. To our knowledge, the safety of NP for large samples over extended periods of time has not been reported.

The Lung Health Study, however, has information on the use of NP from a nonblinded study of 3,094 users. The data on possible side effects of NP were gathered continuously throughout the study, whether participants were using NP, had formerly used NP and then stopped, or were using it again after an interval of

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Table 1—*Baseline Characteristics of the Lung Health Study Sample*

Characteristic	Special Intervention (n=3,923) Mean	SD	Usual Care (n=1,964) Mean	SD
Gender, %				
Men	62.4		63.8	
Age, yr				
Men	48.5	7.0	48.3	6.9
Women	48.5	6.5	48.6	6.6
Married, %				
Men	78.1		76.5	
Women	61.8		57.0	
Education beyond high school, %				
Men	61.1		62.6	
Women	51.3		52.8	
Cigarettes per day				
Men	31.1	14.3	30.9	14.5
Women	27.0	12.6	27.2	13.0
Pack-years				
Men	43.1	20.4	42.8	19.4
Women	36.3	16.3	37.0	17.3
Previous use of NP, %				
Men	34.1		36.6	
Women	42.4		46.7	

not using it, and whether participants reported smoking or not smoking while using NP.

The purposes of this analysis of Lung Health Study data are as follows: (1) to assess the rate of occurrence of cardiovascular deaths and cardiovascular conditions resulting in hospitalization associated with the use of NP during the 5 years of the study; (2) to describe the reported side effects attributed to NP at each regular follow-up visit in a 12-month period by the participants using it; (3) to describe the symptoms associated with cessation of NP use for all instances where NP cessation was reported as due to unpleasant side effects; (4) to compare the rates of reported NP problems among those who were concomitant users of NP and cigarettes, to those who were not; and (5) to describe the incidence of problems possibly related to NP use, reported by participants assigned to a smoking cessation intervention who were current NP users at annual follow-up visits (intensively instructed and monitored in its use) and compare them to reports of the same conditions by participants assigned to the usual care control group reporting NP use (minimally instructed and monitored in its use).

Materials and Methods

The Lung Health Study was a randomized multicenter clinical trial sponsored by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute (NHLBI). The main objective of the trial was to determine whether a program encompassing intensive smoking intervention and use of an inhaled bronchodilator could, over a 5-year period, reduce the rate of decline in pulmonary function and reduce respiratory morbidity in middle-aged smokers with mild to moderate airflow obstruction. The detailed design and the primary results of the trial have been reported.[5,6]

Sample

Participants in the Lung Health Study were male and female cigarette smokers, aged 35 to 60 years, with evidence of early-stage COPD. That is, based on baseline spirometry, the ratio of FEV_1 to FVC was no greater than 70% and baseline FEV_1 values were between 55% and 90% of predicted normal.[7] Additional criteria for inclusion in the study included willingness to participate in a smoking cessation program. Exclusion criteria included serious health conditions that were likely to affect lung function, including heart attack within the past 2 years, angina, heart failure, and stroke within the past 2 years. At each clinical center, an appropriate institutional review board approved the project. Participants read and signed a consent form before being enrolled in the project.

A total of 5,887 participants who met all of the eligibility criteria were enrolled at ten clinical centers.[8] They were randomized into one of three groups: special intervention with double-blind assignment to either bronchodilator (ipratropium bromide) or placebo inhaler therapy (a total sample of 3,923 in these two groups) or usual care (a sample of 1,964). The special intervention groups received a behavioral smoking cessation intervention. For the purposes of this analysis, participants are considered to be in either special intervention (smoking cessation intervention and inhaler use) or usual care groups, since no lasting effect of the inhaler therapy was found.[6]

The group intervention program used a multicomponent approach with standard cognitive-behavioral strategies such as stimulus control, avoidance, role playing, assertiveness training, reinforcement, and relaxation techniques.[9] Nicotine replacement medication (Nicorette, 2 mg; Marion Merrell Dow) was used. Participants were strongly encouraged to use NP after quitting smoking, and were instructed and monitored in its proper use. NP use was demonstrated and reviewed regularly in the 12 meetings of the group program. The 12 meetings took place over 3 months with each meeting lasting approximately 1.5 h. At each meeting, participants were asked whether any problems had occurred. Anyone reporting problems was asked to describe or demonstrate their manner of use, as appropriate, and advised about changes that might alleviate the problems. Recommended changes ranged from a simple review of the chew and park procedure, or a temporary reduction or suspension of use, to referral to a study physician when severe problems were reported. NP was distributed free of charge to special intervention study participants. Participants adopted their own preferred level of use within the package insert guidelines and with the advice of their health educator. After the completion of the group program, from study month 4 onwards, participants still using NP returned to the clinic as often as necessary to replenish their supply. The study protocol assumed that most participants would have stopped using NP by 6 months after they had quit smoking. In the special intervention group, 3,094 participants (79%) used NP for various durations in the first year of the study. After 1 year, 1,042 special intervention participants (31%) were using NP.

Following the group smoking cessation program, regular maintenance programs were scheduled each month for the next 4 years or until interest waned in each clinic to support abstinence from smoking. Included among these events were programs on the subjects of weight management, stress management, and exercise. An extended group intervention program was provided to those participants who had relapsed and wished to try again to quit smoking. NP was also provided in this program.

Measures

Special intervention participants were seen at the clinics for the 12-week group smoking cessation program, followed by in-person or telephone contacts typically scheduled at least monthly in the first

year. In addition, at 4-month intervals from randomization, participants were scheduled for interim visits to the clinics for the purposes of bronchodilator canister replacement, measurement of carbon monoxide (CO) in expired air and body weight, self-report of smoking status and inhaler use, and intervention counseling as required, including review of and guidance in NP use techniques.

Smoking status at 4-month intervals was assessed by self-report and CO in expired air (<10 ppm vs ≥10 ppm). Salivary cotinine was sampled at baseline and at annual visits. Self-report, CO, and cotinine indicators of smoking status in the Lung Health Study provided substantially the same results.[10] The following analysis relies on self-reports of smoking for the analysis of self-reported symptoms and on biochemically verified smoking status for analysis of documented cardiovascular events.

At regular 4-month intervals, participants were asked, "While using nicotine gum in the past 4 months, have you experienced any problems which you feel may have been caused by or associated with the gum?" This question was asked in support of monitoring and instruction of NP use. They were not prompted with a list of problems. If participants stopped using NP, they were systematically asked why they had done so. At annual follow-up clinic visits, participants were also asked about their history of illnesses and symptoms, irrespective of their pattern of NP use. A list of illnesses and symptoms was read to them.

At annual visits, all participants were asked, "Have you been hospitalized since your last attended annual visit?" For every hospital admission for which participant consent was given, an admission registration record, physician's discharge summary, operative reports, pathology reports, and radiology reports were requested from the hospital. Records that contained significant mention of cardiovascular, cancer, or respiratory conditions, whether or not these conditions were indicated as a major cause for the hospitalization, were forwarded to a mortality and morbidity review board. This board, an independent panel of three physicians with specialties in respiratory disease, cardiovascular disease, and cancer, provided assessments of the primary causes of forwarded hospitalizations and all deaths. The board was blind to the participant's treatment condition. This analysis will focus only on those hospitalizations and deaths determined to have been due to cardiovascular disease.

Results

Baseline characteristics of the special intervention and usual care samples are displayed in Table 1. More than one third of the participants had previously used NP. There were only minor differences at baseline between the special intervention and usual care groups. There were a number of gender differences. Women in these samples were less likely than men to be married (60.2% vs 77.6%, χ^2 [1]=200.78; p<0.001), they were less likely to have education beyond high school (51.8% vs 61.6%, χ^2 [1]=54.25; p<0.001), had fewer pack-years of smoking (36.4 vs 42.9, t [5,883]=12.75; p<0.001), and were more likely to have previously used NP (43.8% vs 34.9%, χ^2 [1]=46.26; p<0.001). No adjustment for multiple testing has been made to these univariate tests or those that follow.

The use of NP by special intervention participants is described in Figure 1. Cross-sectional levels of use are shown for each scheduled clinic visit, along with the mean number of pieces of 2 mg of NP per day for those using NP, separately for smokers and exsmokers. Two thirds of the special intervention participants who had quit smoking used NP at the beginning of the study. About a third of the special intervention participants, assigned to quit smoking, were unsuccessful at quitting but still reported the use of NP. Smoking status for Figure 1 is based on a positive response to the ques-

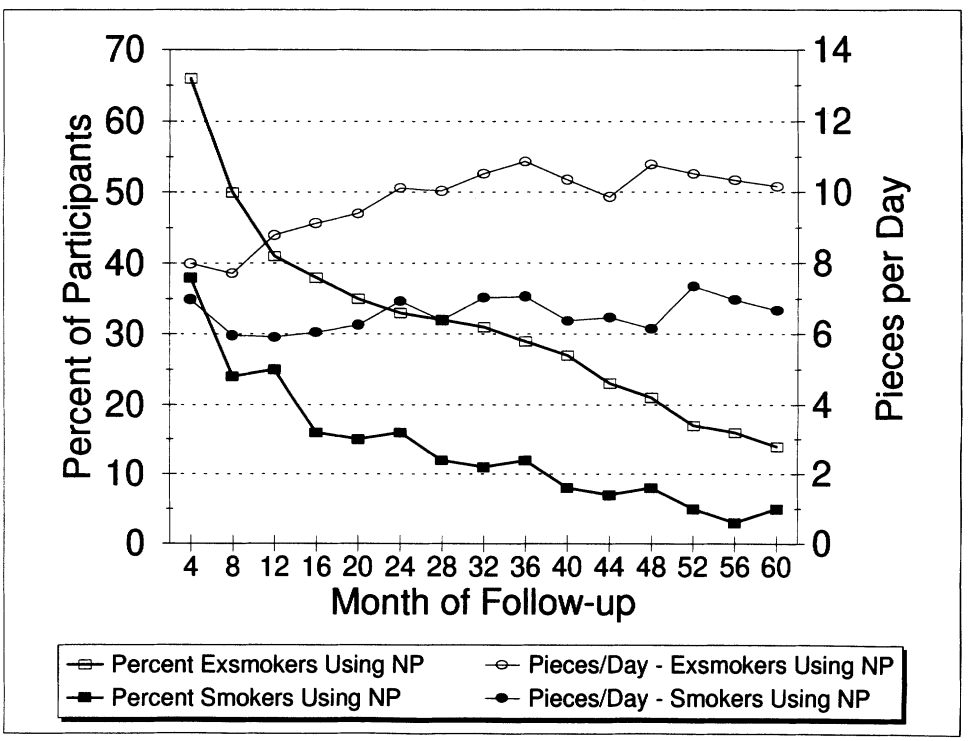

Figure 1. Percent and mean amount of reported use of NP by special intervention smokers and exsmokers.

Table 2—*Frequency Distribution of Fatal and Nonfatal Cardiovascular Events Among Special Intervention Participants

Type of Event	Cause	No. (%) of Events
Hospitalization		188 (91)
	Myocardial Infarction	55 (27)
	Angina	6 (3)
	Ischemic heart disease	47 (23)
	Congestive heart failure	3 (1)
	Other CHD	2 (1)
	Stroke	10 (5)
	Transient ischemic attack	5 (2)
	Arrhythmia	12 (6)
	Pulmonary embolism	6 (3)
	Hypertension	1 (0)
	Other CVD	40 (19)
Death		19 (9)
	Myocardial infarction	4 (2)
	Ischemic heart disease	3 (1)
	Stroke	2 (1)
	Pulmonary embolism	1 (0)
	Other CVD	4 (2)
	Sudden cardiac	5 (2)

*First occurrence of hospitalization or death from causes related to cardiovascular disease. CHD=coronary heart disease; CVD=cardiovascular disease.

tion, "Do you now smoke cigarettes (*ie*, one or more per week)?" and use of NP by, "Do you now use nicotine gum (Nicorette)?" These questions create a relatively inclusive definition of concomitant use, where individuals who had alternated between smoking and attempts to quit using NP during the same week would be counted as concomitant users. By the end of the study, 5% of participants unsuccessful at quitting smoking were using NP, compared with 14% of exsmokers. Among exsmokers, the level of use trended upwards over the course of the study from eight to ten pieces per day. The level of use by smokers ranged between six and seven pieces per day.

Cardiovascular Conditions

Cardiovascular events that occurred among special intervention participants, regardless of NP use and smoking status, are described in Table 2. Events are shown in the way they are used by a proportional hazards regression. That is, only the first occurrence (be it hospitalization or death) for each participant is shown.

Hospitalization rates for cardiovascular conditions among special intervention participants classified by biochemically verified (by CO) smoking status and reported NP use are shown in Table 3. Among exsmokers, the rates appear uniformly higher for those who were *not* using NP. Among smokers, the rates for NP users appear higher in some years, and the rates for NP nonusers appear higher in others.

Proportional hazards regressions were performed to study predictors of death or hospitalization due to cardiovascular disease among the 3,332 special intervention participants for whom a complete set of first 4-month data was available.[11] NP use was not significantly related to outcome (p=0.53) in a model adjusted for smoking status, gender, age, and baseline diastolic BP. The addition to this model of a term for the interaction of NP use and log of follow-up time (as days following the first 4-month visit) resulted in coefficients that were suggestive of, but not significantly associated with, an initial protective effect of NP that attenuates over time (Table 4). Neither the NP use coefficient nor the coefficient for the interaction term were statistically significant, but the suggested effect is similar to that seen by inspection of Table 3, where the initially low rates of hospitalization among NP users slightly increase over time, relative to the nonusers, particularly among exsmokers. A model that substituted NP dose (reported pieces per day at clinic visits) for NP use led to the same conclusions. Neither NP

Table 3—*Hospitalization Rates* for Cardiovascular Conditions Among Special Intervention Participants† by Year in Study, Use of NP, and Use of Cigarettes*

	Exsmokers‡				Smokers			
Time in Study, mo	NP Users	N	NP Nonusers	N	NP Users	N	NP Nonusers	N
4-12	1.27	1,243	6.54	641	0.91	550	4.65	887
12-24	0.53	526	2.85	807	7.07	466	5.67	1,507
24-36	4.38	419	7.34	864	11.76	329	5.62	1,667
36-48	3.72	370	5.78	929	5.12	219	6.02	1,726
48-60	2.29	265	6.44	1,054	9.10	134	6.69	1,748
Overall	2.23		5.78		6.40		5.87	

*Hospitalizations per 100,000 person-days. Includes multiple hospitalizations per person (up to eight) that occurred between the first 4-month visit and the last attended follow-up visit.

†N=3,321 special intervention participants who attended at least one annual visit and for whom complete data for the first 4-month visit were available.

‡Categories for smoking and gum use are determined at the start of each 4-month interval. Data are shown only for visits conducted within ±2 months of the anniversary date. Missing data were handled as follows: participants missing smoking information were assumed to be smoking, and participants missing gum information were assumed to be not using gum.

Table 4—*Proportional Hazards Regression* Predicting Fatal and Nonfatal Cardiovascular Events Among 3,332 Special Intervention Participants*

Covariate	Coefficient	SE	Risk Ratio	95% CI	p Value
NP use†	-1.915	1.152	0.15	(0.02, 1.41)	0.10
Current smoker†	0.473	0.150	1.61	(1.20, 2.16)	0.002
NP use by Log time†,‡	0.286	0.180			0.11
Gender (Risk=male)	0.926	0.179	2.52	(1.78, 3.59)	<0.0001
Age (Risk/decade)	0.759	0.115	2.14	(1.71, 2.68)	<0.0001
Diastolic BP (Risk/10 mm Hg)	0.186	0.078	1.20	(1.03, 1.40)	0.02

*Stratified on Lung Health Study clinic.

†Entered as a time-dependent covariate. Categories for smoking and gum use are determined at the start of each four-month interval. Data were used only from visits conducted within ±2 months of the anniversary date. Missing data were handled as follows: participants missing smoking information were assumed to be smoking, and participants missing gum information were assumed to be not using gum.

‡"Time" is entered as number of days of follow-up after the first 4-month visit.

dose nor the interaction between NP dose and log of follow-up time were statistically significant. An increased risk associated with concomitant use of NP and cigarettes might have been detected by a significant interaction between NP use and smoking. This interaction was included, but was not significant (p=0.63).

To assess a possible effect of assignment to active vs placebo inhaler groups on the cardiovascular risk associated with NP use, or on the NP by log of follow-up time interaction, the Table 4 analysis was repeated, including an inhaler assignment term and the interaction terms. There was not a significant interaction between inhaler assignment and NP use, or between inhaler assignment and the NP use by log of follow-up time interaction. Proportional hazards regressions were also performed to study predictors of death from all causes, and neither NP use nor the interaction between NP use and log of follow-up time were significantly related to outcome.

Peptic Ulcers

Special intervention participants who reported a history of peptic ulcer were not eligible to receive NP from the Lung Health Study, unless a prescription was provided by their primary care physician. Excluding these participants, a proportional hazards regression was used to assess the extent to which the use of NP may have contributed to the incidence of new ulcers. During the 5 years of the study, there were 116 self-reported new ulcers. NP use, cigarette smoking, gender, and age were included in the model. NP was found to have a nonsignificant protective effect against peptic ulcers (p=0.06; risk ratio=0.63). Further analysis found no effect of NP dose, or of the interaction of either NP use or NP dose with log follow-up time on the occurrence of peptic ulcers.

Table 5—*Percent of Special Intervention NP Users Reporting Symptoms for Past 4 Months at the First 4-Month Visit Classified by Gender*

Symptom	Male	Female
Belching	1.0	1.1
Craving a cigarette	0.3	0.3
Dizziness	0.5	0.3
Excessive salivation	0.4	0.6
Headache	0.5	0.6
Hiccups	2.8	3.8
Indigestion	5.1	3.9
Insomnia	0.1	0.0
Irritability	0.2	0.1
Jaw muscle ache	1.6	1.2
Loss of appetite	0.1	0.0
Mouth irritation	6.2	6.5
Mouth ulcers	4.0	5.3
Nausea	1.8	3.8
Throat irritation	2.2	2.8
Other symptoms	7.4	7.0
No symptoms reported	73.1	71.2
Sample size	1,797	1,146

Rates of Reporting Symptoms

Analysis of self-reported symptoms emphasizes the first 4 months of the study when NP use levels were at their highest. The percent of special intervention NP users reporting symptoms that they attribute to their NP use is shown in Table 5 tabulated by gender. The symptoms shown were listed on the 4-month questionnaire, but were not read to the participant by the interviewer. The levels of reporting any symptoms were modest, and rarely exceeded 5%. No gender differences in symptom reporting rates are found in Table 5 (χ^2). Rates of symptom reporting were also classified by level of education (high school or less vs more than high school). No differences were found.

The list of symptoms in Table 5 was related to the level of use of NP coded as follows: up to 5 pieces per day, 6 to 10 pieces, 11 to 15 pieces, and 16 or more pieces. Among male NP users in the first 4 months, NP was used at these four levels by 407, 427, 197, and 76 individuals, respectively. Level of NP use was tested against rates of reporting for each symptom on the list. Level of NP use was related to rates of reporting jaw muscle ache and hiccups. In men, jaw muscle ache was reported in 0%, 2.3%, 4.1%, and 5.3% of the four levels of use (χ^2 [3]=17.06; p<0.001). For hiccups the rates were 2.0%, 3.3%, 6.6%, and 1.3% (χ^2 [3]=10.06; p<0.05). Among female NP users, NP was used at the

Table 6—*Percent of Special Intervention NP Users Reporting Symptoms for Past 4 Months at the First 4-Month Visit by Whether They Quit Treatment With the Medication Due to Side Effects, for Those Symptoms That Differed Between the Groups*

Symptom	Not Quit	Quit Due to Side Effects	Difference	95% CI for Differences
Mouth irritation	5.5	22.2	16.7	12.6-20.8
Other symptoms	6.5	21.5	15.0	10.7-19.4
Mouth ulcers	3.7	20.1	16.4	12.9-19.9
Indigestion	4.0	16.7	12.7	9.1-16.2
Nausea	1.9	16.0	14.1	11.4-16.7
Headache	0.3	4.9	4.6	3.3-5.8
Sample size	2,799	144		

four levels by 279, 248, 136, and 35 individuals, respectively. Belching was the only symptom significantly related to level of use. The rates were 0%, 1.6%, 0%, and 5.7% (χ^2 [3]=14.93; p<0.01).

NP Discontinuance Due to Side Effects

At the regular clinic visits, special intervention participants who had discontinued using NP in the previous 4 months were asked why they had done so. Those who responded after the first 4 months that it was due to "unpleasant side effects" are shown in Table 6 compared with other NP users. The side effects identified significantly more frequently by those discontinuing NP use included mouth irritation, mouth ulcers, indigestion, nausea, headache, and other symptoms not listed. Because Table 6 repeatedly uses the 95% confidence interval (CI), small differences should be interpreted with caution.

Concomitant Use of NP and Cigarettes

To assess the extent to which concomitant use was associated with an elevated rate of reported side effects, we compared the rates of reporting of NP symptoms at the 4-month visit by the 389 smoking and 2,554 nonsmoking NP users. None of the symptoms individually or combined were significantly different between the two groups.

Monitoring and Instruction of NP Use

The special intervention group received an intensive smoking cessation program that included intensive instruction in the use of NP and follow-up monitoring of its use. Participants in the usual care group were left to seek their own help in quitting smoking, and a few of them (n=49 at year 1) obtained NP from their private physician. It was assumed that usual care NP users were exposed to much less intensive NP instruction and monitoring than special intervention NP users.

Table 7 compares the rates of reporting of symptoms for the previous 4 months by special intervention and usual care men and women at the first annual clinic follow-up visit. While participants at the 4-month visit were asked whether they associated any problems with their NP use, and were not prompted with the symptom list, the data in Table 7 were obtained by asking whether each individual symptom had occurred, and without specific reference to NP use. Higher rates of reporting were produced by this procedure. For example, at the 1-year visit, 13.7% of male respondents named one or more NP symptoms when not prompted, but 71.4% responded when the entire list was read to them, and not associated specifically with the use of NP. The corresponding rates for female respondents were 15.3% and 82.5%.

As shown in Table 7, usual care participants reported some of the prevalent symptoms significantly more often than did special intervention participants. Usual care men reported dizziness and throat irritation significantly more often than special intervention men did (χ^2). Usual care women reported headache and throat irritation significantly more often than special intervention women did. These symptoms were reported two or three times as often by usual care participants as by special intervention participants.

Discussion

There have been a number of previous reports of the side effects associated with using NP. The sample size of NP users in the Lung Health Study, however, is an order of magnitude larger than that in previous reports. This enables the classification of users in a number of ways to provide detailed analyses not previously possible.

Table 7—*Percent of NP Users Reporting Symptoms for Past 4 Months at the First Annual Follow-up by Gender and Group Assignment*

Symptom	% Men Reporting		% Women Reporting	
	Special Intervention	Usual Care	Special Intervention	Usual Care
Belching	19.0	17.4	18.9	33.3
Dizziness	11.8	34.8*	23.3	37.0
Excessive salivation	5.3	4.4	8.3	11.1
Headache	17.1	30.4	34.2	59.3†
Hiccups	12.3	8.7	15.6	14.8
Indigestion	20.7	17.4	22.8	29.6
Insomnia	18.4	17.4	31.1	48.2
Irritability	31.3	34.9	36.9	55.6
Jaw muscle ache	11.2	13.0	18.1	14.8
Loss of appetite	3.4	0.0	6.1	7.4
Mouth irritation	14.2	17.4	23.1	25.9
Mouth ulcers	8.5	4.4	11.9	11.1
Nausea	1.9	4.4	3.9	11.1
Throat irritation	12.1	30.4†	13.1	40.7†
Other symptoms	8.0	13.0	10.6	3.7
Any of the above	71.4	73.9	82.5	92.3
Sample size	527	23	360	26

*p<0.01.
†p<0.02.
‡p<0.02.

To our knowledge, data on hospitalizations for cardiovascular conditions have not previously been presented from a study including NP users and nonusers. The rates reported in this study were low, considering the population of heavy smokers with evidence of early COPD. Further, there was no evidence of a relationship between the dose of NP and cardiovascular conditions.

There seemed to be a protective effect of NP use that dissipated over time. One way of speculating about this mechanism might be as follows. Quitting smoking is presumed physiologically stressful to some extent. NP softens the transition from smoking to abstinence. Some people with borderline cardiovascular disease who quit without NP might then have observable events. Most quitting in the Lung Health Study occurred early, which is where this protective effect may have been more likely to be observed.

The rates of reporting of NP side effects are consistent with previous studies. When users are classified by gender or education, there are no apparent differences. Level of NP use is related to rates of reporting of a few very minor symptoms: jaw muscle ache and hiccups for men and belching for women. Only 5% of NP users reported quitting NP in the first 4 months because of side effects. Indigestion, mouth irritation, and mouth ulcers were both associated with NP discontinuance and were reported by 5% or 6% of all NP users.

More than one third of our special intervention participants reported having used NP before joining the Lung Health Study. Most of these participants probably had little or no previous trouble with it if they were willing to use it again. The symptom rates reported herein may be lower than rates for a sample consisting entirely of first-time NP users.

Although users of NP were instructed not to smoke while using NP, about 12% of our special intervention participants reported doing so at their first 4-month clinic visit. Clearly the efficacy of NP as a part of the process of quitting smoking was nullified in those who smoked and used NP concomitantly. It has also been suggested that concomitant use is dangerous to health. Although this study was not designed to test this in detail, we found no evidence of it. Since serum nicotine levels in venous blood of people using typical amounts of 2 mg NP amount to only about one third of those found in cigarette smokers, concomitant use is unlikely to produce a dramatic increase in nicotine level.[12,13]

In the Lung Health Study, those reporting concomitant use of NP and cigarettes may have been motivated to minimize reports of side effects in order to get an additional supply of NP, since the study protocol prohibited dispensing of NP to those who reported concomitant use. This bias in symptom reporting, if it occurred, would have been more prevalent in later months in the study. The data we relied on to assess symptoms associated with concomitant use were collected at the first 4-month follow-up, that is, the first formal clinic visit after the smoking cessation program ended. Participant awareness of constraints on NP availability would have developed during this visit after they had completed the questionnaire, and later in the program. In the regression analysis, an effect of concomitant use might have been detected as a significant interaction term between NP use and smoking. This interaction was not found to be significant.

The Lung Health Study provided a unique opportunity to compare two groups that were equivalent at baseline. The NP using subset of one had intensive instruction and monitoring of NP use (special intervention). The NP users in the other likely did not (usual care). We found that several symptoms were two or three times more prevalent among the usual care NP users. It has previously been reported that intensive instruction and follow-up of NP use significantly increase its effectiveness as an aid to smoking cessation. This is the first evidence we are aware of that indicates that intensive instruction and monitoring may also significantly reduce the rate of reporting of side effects.

Another difference between our special intervention and usual care groups with respect to NP use was that usual care participants would have generally paid for their NP, while special intervention participants did not. Special intervention participants likely used more NP as a consequence. In addition, special intervention participants were actively encouraged to use NP as a part of the intervention program. If a difference in level of use existed, and consequently biased the rates of symptom reporting, we would have expected the bias in the direction of more symptoms reported by special intervention participants. However, in our comparison of special intervention and usual care symptoms, we found fewer symptoms reported by special intervention participants, which supports the value of instruction and monitoring for reducing symptoms.

NP will continue to be used as an aid to smoking cessation. Although the nicotine patch has some advantages, there will be those who prefer NP or whose skin reacts to the patch. Based on an analysis of both hospitalization data and symptoms in relation to NP use, we found no evidence of serious side effects. In addition, our data suggest that instruction and monitoring of NP use may be important in minimizing side effects and in maximizing its usefulness as nicotine replacement medication.

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