Research Article

Reduced Nicotine Content Cigarettes and Nicotine Patch

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Abstract

Background: Reduced nicotine content (RNC) cigarettes have led to smoking fewer cigarettes, withdrawal relief, and facilitation of cessation. The aim of this study is to examine the effects RNC cigarettes with and without nicotine patch and patch alone on smoking behavior, toxicant exposure, withdrawal discomfort, and as an exploratory analysis, on long-term abstinence.

Methods: This study involved a randomized, parallel arm design and six weeks of: (i) 0.05–0.09 mg nicotine yield cigarettes ($N = 79$); (ii) 21 mg nicotine patch ($N = 80$), or (iii) 0.05–0.09 nicotine yield cigarettes with 21 mg nicotine patch ($N = 76$); all groups received six weeks of additional behavioral treatment with follow-ups up to six months.

Results: Combination approach led to lower rates of smoking assigned cigarettes and hence lower carbon monoxide levels than RNC cigarettes alone. In addition, the combination approach was associated with less withdrawal severity when switching from usual brand to assigned product, and less smoking of usual brand cigarettes during treatment, but not after treatment compared with the other approaches.

Conclusion: Combining very low nicotine content cigarettes with nicotine patch may improve the acute effects resulting from switching to either of these products alone.

Impact: These findings may have implications for smoking cessation treatment or a policy measure to reduce nicotine content in cigarettes. *Cancer Epidemiol Biomarkers Prev; 22(6); 1015–24. ©2013 AACR.*

Introduction

The use of reduced nicotine content (RNC) cigarettes has been considered as a possible cessation tool and as a national policy measure (1–3). Unlike "light" cigarettes, the nicotine content in the RNC cigarette itself is substantially lower than conventional cigarettes. Reducing nicotine in cigarettes to levels that are nonaddictive would potentially lead to cessation from smoking (because cigarettes are no longer reinforcing) and if implemented as a policy, has the potential to have significant public health benefit.

To date, the scientific literature shows that switching to RNC cigarettes leads to a reduction in cigarette intake with minimal compensatory smoking behavior, no greater exposure to toxicants than their usual brand cigarettes, decrease in dependence and facilitation of abstinence among smokers not interested (4, 5), and interested in quitting smoking (3, 6). As an example of the effects of RNC cigarettes in facilitating cessation, smokers interested in quitting who were assigned to the 0.05 mg nicotine yield cigarettes achieved a biochemically verified 7-day point prevalence smoking cessation rate of 35.9% as compared with 13.5% and 20.0% among those smokers assigned to a higher nicotine yield cigarettes (0.3 mg nicotine yield) or to nicotine lozenge at 6 weeks posttreatment, respectively. Another large study found that smokers calling a quit line and assigned to RNC cigarettes plus usual care, which involved use of nicotine replacement therapy (NRT), were observed to have significantly higher abstinence rates than those who were provided usual care alone (3). To date, no study has examined the effects of combining RNC cigarettes plus nicotine patch on smoking behavior, resultant toxicant exposure, withdrawal symptoms and craving, dependence scores, and on abstinence rates compared with medicinal nicotine product alone and with RNC cigarettes alone. To address this gap, we conducted a study in which smokers were randomized to 6 weeks of 0.05–0.09 mg nicotine yield cigarettes, 21 mg nicotine patch, or a combination of both. We hypothesized that smoking behavior, toxicant exposure, withdrawal, and craving upon switching to the assigned product would be less for the combined intervention condition compared with the products alone. These hypotheses are based on the assumption that the RNC cigarettes would decrease craving associated with the sensory aspects of smoking and reduce the reinforcing value of cigarettes, whereas the patch would provide nicotine (not associated

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with the act of smoking) for nicotine-related craving and withdrawal relief. Therefore, the combination therapy would lead to better treatment response than either product alone. In an exploratory analysis, we also hypothesized that abstinence rates would be highest with combined product treatment condition compared with the single product conditions.

Our goal was to examine the feasibility of using these cigarettes as a method to significantly reduce smoking behavior and the effects of adding the nicotine patch in augmenting beneficial effects from RNC cigarettes. If this combination approach proved more effective than the products alone, then RNC cigarettes can be considered an adjunct to existing NRTs. In addition, in the event of a national policy to reduce nicotine in all cigarettes, the results would suggest the importance of making NRTs easily accessible to smokers.

Materials and Methods

Subjects

Smokers between the ages of 18 and 70 interested in quitting smoking were recruited via advertisement from the Twin Cities and Duluth, Minnesota. In the advertisements, the study was described as testing a nicotine-free cigarette or new tobacco product as a way to become smoke free. To be eligible, smokers had to (i) have smoked 10 to 40 cigarettes daily for the past year (the range was instituted to reduce heterogeneity); (ii) be in good physical and psychiatric health; and (iii) have no contraindications for medicinal nicotine use. Smokers using other tobacco or nicotine products and smokers who were pregnant or nursing were excluded. The study was approved by our Institutional Review Board and in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Study design

After a telephone screening to determine preliminary eligibility, an orientation session was held at which the study was further explained, written informed consent was obtained, and a more thorough screening for eligibility was conducted.

After a 2-week period during which baseline measurements were collected while subjects smoked their usual brand *ad libitum*, subjects were assigned to one of 3 conditions: (i) 0.05–0.09 mg nicotine yield cigarettes, that is very low nicotine content (VLNC) cigarettes, (ii) 21 mg nicotine patch, or (iii) combination of both. Subjects were initially assigned Quest 3 cigarettes (manufactured by Vector), a commercially available VLNC cigarette of $\leq$ 0.05 mg machine-determined nicotine yield, 0.7 to 0.9 mg nicotine and about 8 to 11 mg tar on per cigarette basis, and with reduced levels of tobacco-specific nitrosamines compared with conventional cigarettes [4-(methylnitrosamino)-I-(3-pyridyl)-1-butanone (NNK) = 0.05 and *N*-nitrosonornicotine (NNN) = 0.83 μg/g tobacco wet weight for Quest 3 vs. NNK = 0.68 and NNN = 2.8 μg/g tobacco wet weight for Marlboro "Light" (7)]. Quest 3 cigarettes no

longer were available after randomizing 27% of our subjects, so we switched to Xodus (manufactured by 22nd Century Limited, LLC), which contained 0.09 mg machine-determined nicotine yield, 1.2 mg nicotine, about 10 mg tar and similarly low carcinogens (e.g., NNK = 0.05 μg/g and NNN = 0.72 μg/g tobacco wet weight, unpublished data). The average nicotine yield per each cigarette puff was about from 0.005 to 0.008 and 0.010 to 0.011 mg, for the 0.05 and 0.09 mg nicotine yield cigarettes, respectively. Subjects were instructed to use only assigned products for 6 weeks, after which time they were to discontinue all product use. Subjects were seen weekly during the 6-week product assignment period and an additional 6 weeks at weeks 7, 8, 10, and 12 for continued behavioral treatment.

At each visit, subjects assigned to either cigarette condition were provided a supply equivalent to 150% of their baseline smoking rate (to allow for compensatory smoking) and were told to smoke these VLNC cigarettes *ad libitum*, that is, as they would smoke their usual cigarettes. Subjects assigned to receive nicotine patch were informed to replace the old patch with the new patch each morning. Subjects maintained a daily smoking diary where they recorded any cigarettes smoked (either those assigned to them or their usual brand). They were not penalized for smoking unassigned cigarettes, but told that although we do not encourage them to smoke cigarettes other than those assigned, it is crucial to the study that they accurately report all cigarette use.

Brief standardized counseling was provided at each visit during the intervention phase of the study. During the first 6 weeks, subjects assigned to the cigarette conditions were counseled to consider the use of these products as a step toward quitting and discussed behavioral strategies to resist smoking other (non-VLNC) cigarettes. Subjects assigned to the nicotine patch only condition were provided treatment tools recommended by the U.S. Clinical Practice Guideline (8). During the second 6-week intervention phase, all subjects received counseling similar to that received by the subjects assigned to the nicotine patch condition. All 3 treatment groups received similar amounts of behavioral support.

Follow-up visits occurred at 16, 24, and 36 weeks. Subjects who completed the study were paid up to $330.

Outcome measures

Biomarkers of tobacco exposure measures included (i) urinary total nicotine equivalents (TNE), which is the sum of nicotine, cotinine, and 3′-hydroxycotinine and their glucuronides, altogether accounting for 73% to 96% of the nicotine dose (9, 10); (ii) urinary total cotinine, a metabolite of nicotine; (iii) alveolar carbon monoxide (CO) measured using the Bedfont Micro Smokerlyzer (Bedfont Scientific Limited); and (iv) urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), metabolites of the tobacco-specific lung carcinogen NNK (11). All measures were assessed at baseline. In addition, CO was assessed at each clinic visit, cotinine at

weeks 2, 6, and 12 of intervention and at follow-up visits, and biomarkers for other exposures at week 6 of intervention.

Subjective measures included: (i) a Tobacco Use Questionnaire asking about current tobacco use status (cigarettes and other tobacco products); (ii) a daily diary detailing the number of assigned products used and usual cigarettes smoked; (iii) the Minnesota Nicotine Withdrawal Scale, a widely used scale assessing withdrawal from cigarettes (12–14), nicotine gum (15, 16), and smokeless tobacco (15, 17), (iv) Fagerstrom test for nicotine dependence (FTND, 18), (v) Centers for Epidemiological Studies 20-item scale (CES-D) assessing current symptoms of depression (19), and (vi) perceived health risk, a ladder involving rating risk for addiction to a product on a scale ranging from 1 to 10 (6). All of these measures were assessed at baseline. Cigarette or product use was assessed daily, the Tobacco Use Questionnaire and Minnesota Nicotine Withdrawal Scale at each clinic visit, and perceived health risk at weeks 2 and 6.

Statistical analysis

Subjects' baseline characteristics including demographics and smoking history were described and compared among 3 intervention groups. Discrete variables were analyzed using Pearson χ^2 or Fisher exact tests. Contiuous variables were analyzed using either one-way ANOVA or Kruskal–Wallis tests.

We conducted an intention-to-treat analysis. Biomarkers including TNE, cotinine, and NNAL were adjusted for creatinine and analyzed on the natural log scale to ensure normality; geometric means in original units are presented. Abstinence during the first 6-week treatment period was calculated as point prevalence abstinence from usual brand cigarettes for the past 7 days (by self-report). After this period, biochemically verified 7-day point prevalence abstinence and continuous abstinence rates during weeks 12, 16, 24, and 36 were calculated. Differences between treatment groups were evaluated using χ^2 tests. Dropouts were considered to have relapsed at the date of their last follow-up visit. Time to smoking relapse was calculated from the start of treatment to date of first relapse (defined as smoking of >4 usual brand cigarettes during treatment period or any tobacco use during follow-up). Those who remained abstinent throughout the study were censored at the time of last follow-up. Kaplan–Meier methods were used to determine the median time to relapse and 95% confidence interval (CI) for each group.

All continuous outcomes with repeated measures from baseline through treatment were analyzed using mixed effects ANOVA models with fixed effects for site, treatment, visit, interaction between treatment and visit, and a random effect for subject. Least squares (LS) means and 95% CI are presented unless otherwise noted. The P values reported were adjusted for multiple comparisons as appropriate using a Bonferroni correction. $P < 0.05$ were considered statistically significant.

Results

Subjects

Figure 1 shows the consort diagram outlining the disposition of the subjects. Of the 316 who signed the informed consent form, 235 smokers ($n = 203$ from Minneapolis, Minnesota and $n = 32$ from Duluth, Minnesota) were randomly assigned to treatment (80 to nicotine patch, 79 to VLNC, and 76 to VLNC + nicotine patch).

No significant differences in demographics and smoking history, or biomarkers of exposure were observed across the treatment conditions at baseline (see Tables 1 and 2). Of those subjects who enrolled in the study, 173 subjects completed treatment ($N = 60$ in nicotine patch, $N = 55$ in VLNC, and $N = 58$ in VLNC + nicotine patch). The number of dropouts in each group at various stages throughout the study with reasons for dropouts is indicated in Fig. 1. All subjects were contacted for follow-up, accounting for the higher numbers during follow-up compared with the end of treatment. There were no significant differences in baseline characteristics between subjects who dropped out of the study after randomization and those who completed the entire study.

Product use during treatment

The number of assigned cigarettes smoked per day during the first 6-week treatment period is illustrated in Fig. 2A. There were significant treatment ($F_{(2,876)} = 130.88$, $P < 0.0001$), time ($F_{(5,876)} = 36.75$, $P < 0.0001$), and treatment by time ($F_{(10,876)} = 9.81$, $P < 0.0001$) effects observed. Significant differences in number of assigned cigarettes smoked were observed at each time point between the VLNC and VLNC + nicotine patch conditions ($P \leq 0.01$), with the exception of week 1 ($P = 0.063$); those assigned to the VLNC + nicotine patch smoked fewer cigarettes. At week 6, the mean ± SD number of VLNC cigarettes smoked in the VLNC condition was 16.2 ± 10.2 and in the VLNC + nicotine patch condition was 11.3 ± 7.6. Among subjects assigned to the 2 conditions with the nicotine patch, 100% of the nicotine patch group and 95.6% of the VLNC + nicotine patch group reported daily use of the patch at week 6.

Across treatment groups, significant differences in abstinence from nonstudy cigarettes (e.g., usual brand cigarettes) were observed during the 6-week product assignment period ($P = 0.0001$). In particular, those subjects in the VLNC + nicotine patch group were significantly more likely to be abstinent than either the nicotine patch or VLNC only groups ($P = 0.004$ and $P = 0.009$, respectively). Subjects were most likely to smoke usual brand cigarettes during the first week of treatment: 54.2% of those assigned to VLNC cigarettes, 63.8% of those assigned nicotine patch alone, and 41.5% assigned to the combined products group. After week 1, the percentage who reported using usual brand cigarettes ranged from

25.4% to 38.2% (during weeks 2 through 6) in the VLNC cigarette group, 35.6% to 50.8% in the nicotine patch group, and 8.3% to 21.7% in the VLNC + nicotine patch group. Significant differences between groups were observed during each of these weeks (all $P < 0.02$). At the week 6 visit, 32.7% in the VLNC cigarettes group, 43.3%
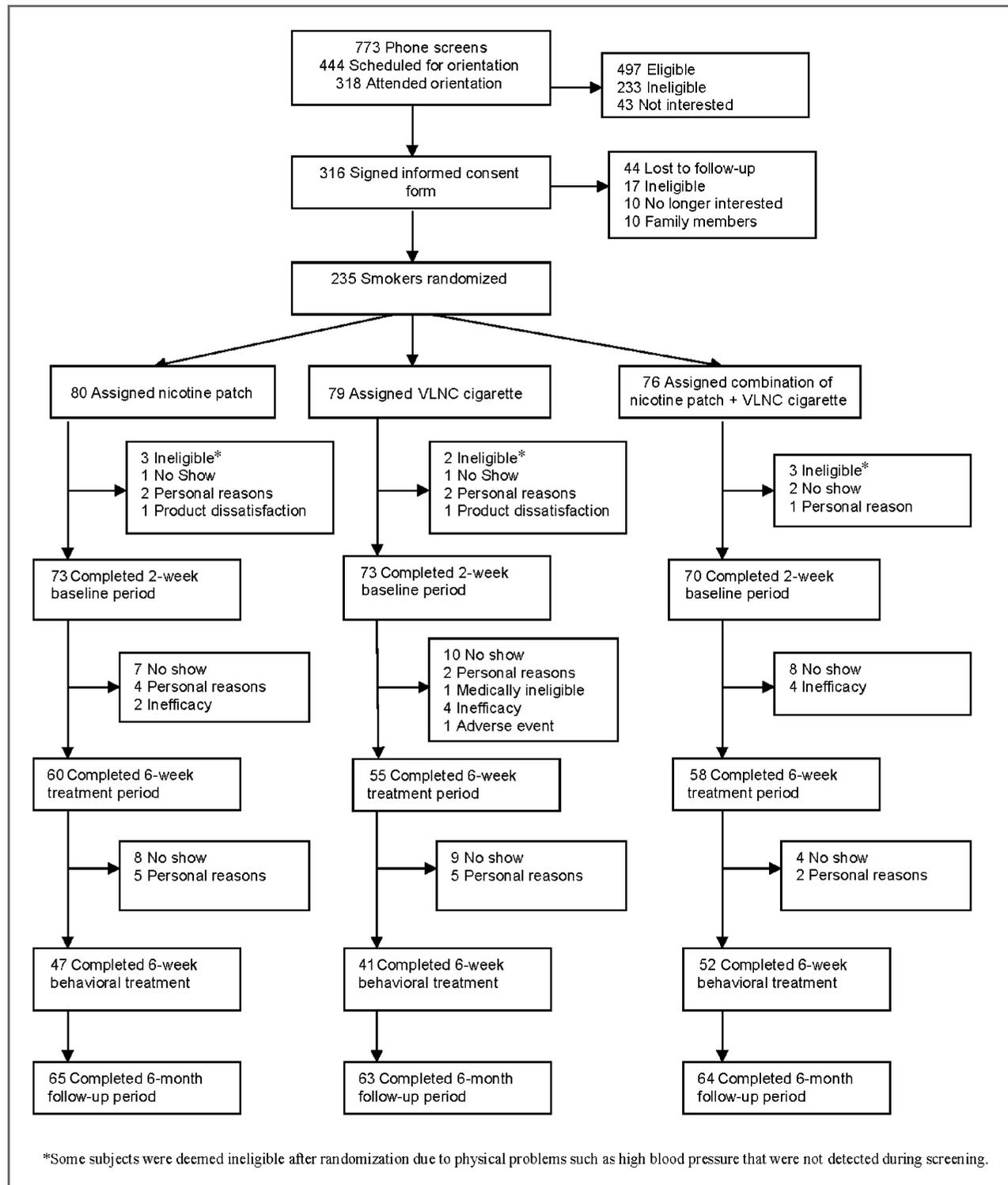

Figure 1. Flow of subjects through study.

Table 1. Baseline demographics and smoking history of subjects by treatment group ($N = 235$)

	Overall	VLNC	NP	VLNC + NP
Age (y)	47.0 ± 11.7	46.5 ± 12.2	47.3 ± 11.0	47.0 ± 11.9
Female	57.9%	59.5%	57.5%	56.6%
Non-Hispanic Whites	82.0%	85.9%	84.8%	75.0%
Education				
8th grade or less	0.9%	2.6%	0.0%	0.0%
Some high school	2.6%	3.9%	1.3%	2.7%
High school graduate	22.8%	18.0%	26.3%	24.0%
Some college/2-year	56.7%	53.9%	58.8%	57.3%
College graduate	13.7%	18.0%	11.3%	12.0%
Graduate	3.4%	3.9%	2.5%	4.0%
Marital status				
Never married	26.8%	25.3%	28.9%	25.3%
Currently married	38.7%	41.8%	36.3%	41.8%
Currently not married	34.5%	32.9%	35.0%	32.9%
Cigarettes per day	18.9 ± 7.2	19.4 ± 6.2	19.5 ± 8.6	17.7 ± 6.3
Duration of having smoked regularly (y)	29.1 ± 12.0	29.2 ± 11.6	29.6 ± 11.7	28.4 ± 12.8
Age becoming a regular smoker (y)	17.9 ± 4.6	17.3 ± 3.6	17.7 ± 4.9	18.8 ± 5.0
Number of quit attempts				
0–2	23.5%	21.6%	22.4%	26.9%
3–5	39.6%	37.8%	40.8%	40.3%
6–10	22.6%	23.0%	22.4%	22.4%
11–20	11.1%	12.2%	11.8%	9.0%
20+	3.2%	5.4%	2.6%	1.5%
Motivation to quit (0–10 scale)	8.5 ± 1.4	8.5 ± 1.4	8.3 ± 1.5	8.6 ± 1.4
FTND	5.4 ± 1.9	5.6 ± 1.7	5.3 ± 2.1	5.1 ± 2.0
CES-D (0–60 scale)	10.6 ± 7.4	11.1 ± 7.7	10.9 ± 7.7	9.6 ± 6.7

NOTE: Because of missing values, the Ns were 217 for quit attempts, 224 for motivation to quit, 227 for FTND and 223 for CES-D. Otherwise, all other variables had data from 233 to 235 subjects.

Abbreviation: NP, nicotine patch.

in the nicotine patch group, and 13.8% in the combined products group reported using such products ($P = 0.002$). Among those reporting smoking nonstudy cigarettes during the treatment period, the mean number of self-reported usual brand cigarettes smoked ranged from 2.8 to at most 4.4 per week.

Effects of products on biomarkers of exposure during treatment

Exhaled CO during the treatment period is shown in Fig. 2B. Urinary TNE, total cotinine, and total NNAL adjusted for creatinine are presented in Table 2.

As illustrated in Fig. 2B, exhaled CO concentrations followed a similar pattern as seen for number of cigarettes smoked per day. There were significant treatment ($F_{(2,847)} = 53.99$, $P < 0.0001$), time ($F_{(5,847)} = 4.88$, $P = 0.0002$), and treatment by time ($F_{(10,847)} = 2.10$, $P = 0.022$) effects. All comparisons between CO levels for each treatment pair at each visit are significantly different from each other ($P \leq 0.05$).

Baseline TNE, total cotinine, and total NNAL levels were significantly higher than levels assessed at week 6 for each of the products (all $P < 0.007$). Compared with subjects

assigned to the VLNC condition, subjects assigned to the nicotine patch and VLNC + nicotine patch conditions had significantly higher TNE levels ($P = 0.0005$ and $P = 0.0001$, respectively) and total cotinine levels ($P = 0.021$ and $P = 0.002$, respectively) at week 6. Subjects assigned to nicotine patch had significantly lower total NNAL than VLNC users at week 6 ($P = 0.024$), but no significant differences were observed between subjects assigned to VLNC + nicotine patch versus VLNC cigarettes ($P = 0.276$).

Effects of products on subjective responses during treatment

Dependence. Perceived heath risk score for addiction during treatment is illustrated in Fig. 3A. Significant decreases were observed across all treatments compared with baseline ($P < 0.0001$); no differences were observed across treatments. Nicotine craving and withdrawal symptoms during the 6-week product assignment period and 1 week after this period are illustrated in Fig. 3B and C. Upon cessation of usual brand cigarettes and switching to the products (week 1 compared with baseline), there was a significant decrease in craving ($P = 0.0002$) and increase in

Table 2. Geometric means of biomarkers at baseline and week 6 of treatment period by treatment groups

Biomarkers	Baseline		Week 6	
	N	Geometric mean (95% CI)	N	Geometric mean (95% CI)
Total TNE[a]				
VLNC Cigarette	54	55.70 (48.42, 64.07)	54	6.89 (4.26, 11.02)
Patch	59	49.90 (43.82, 57.40)	58	23.10 (14.59, 36.60)
VLNC Cigarette + Patch	58	53.52 (46.99, 61.56)	58	27.39 (17.29, 43.38)
Total cotinine[a]				
VLNC cigarette	54	17.12 (14.44, 20.09)	54	2.03 (1.20, 3.45)
Patch	59	16.78 (14.30, 19.69)	59	5.50 (3.31, 9.13)
VLNC cigarette + patch	58	17.99 (15.33, 21.12)	58	7.65 (4.59, 12.76)
Total NNAL[b]				
VLNC cigarette	53	1.20 (1.00, 1.43)	52	0.40 (0.29, 0.55)
Patch	59	1.29 (1.09, 1.53)	59	0.25 (0.18, 0.34)
VLNC cigarette + patch	57	1.09 (0.92, 1.30)	55	0.26 (0.19, 0.36)

NOTE: Values are for all subjects from whom data were collected at the visit in question.
[a]nmol/mg creatinine.
[b]pmol/mg creatinine.

withdrawal symptoms ($P < 0.0001$) across all 3 treatment groups. For craving, no significant differences were observed between treatments. Increase in nicotine withdrawal scores upon cessation of usual brand cigarettes was significant by treatment group ($P = 0.008$); those assigned to VLNC + nicotine patch had significantly lower withdrawal symptoms than nicotine patch alone ($P = 0.008$), but only borderline significantly lower than VLNC alone ($P = 0.092$). No differences were observed between nicotine patch versus VLNC alone. Upon cessation of the product (week 7 compared with week 6), a significant increase in craving was observed ($P < 0.0001$), but no differences among treatments. For withdrawal symptoms, a significant change was observed ($P < 0.0001$), with withdrawal symptoms lower in week 7 compared with week 6 for those assigned to the nicotine patch and slightly higher in week 7 for those assigned to the VLNC or VLNC + nicotine patch groups. These differences were not quite statistically significant among treatments ($P = 0.110$).

Abstinence

After completion of the assigned product treatment period, biochemically verified (CO < 6 ppm to rule out cigarette use) point prevalence rates of abstinence from cigarettes at each of the follow-up visits and continuous abstinence rates (at weeks 12, 24, and 36) showed no significant differences across treatment groups (Table 3). Similar results were observed for abstinence from all nicotine-containing products (CO < 6 ppm, cotinine < 35 ng/mL). If subjects who never received the product were excluded from the analysis, the rates of point prevalence abstinence at week 36 across the conditions would range from 19.2% to 21.4%. The median time to relapse (95% CI) since treatment onset was 7.1 (6.7–7.7) weeks for VLNC + nicotine patch, 2.6 (1.7–5.9) weeks for VLNC, and 2.1 (1.6–3.9) weeks for nicotine patch.

Discussion

The combination of VLNC + nicotine patch led to significantly lower rate of smoking assigned cigarettes and hence lower CO levels compared with VLNC
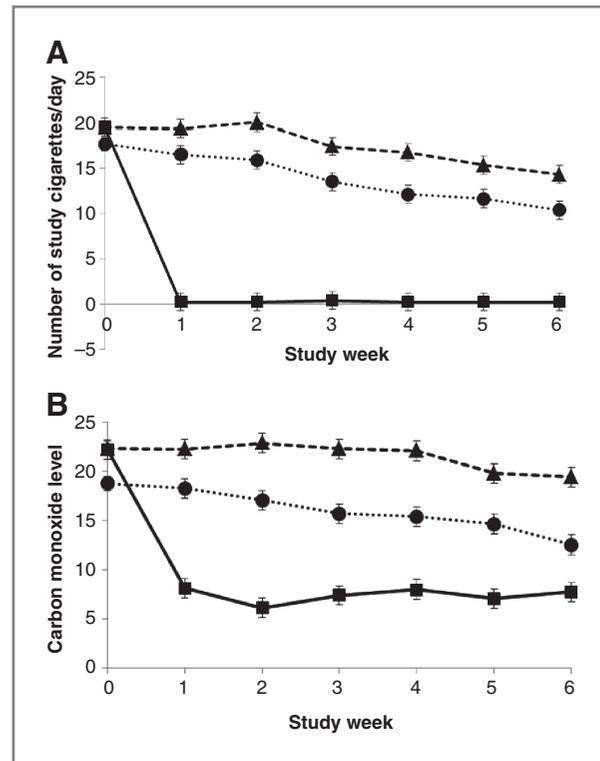

Figure 2. LS mean (±SE) of number of study cigarettes smoked per day (A) and exhaled carbon monoxide (B). Triangle represents VLNC cigarette alone; square represents nicotine patch alone; circle represents VLNC + NP.
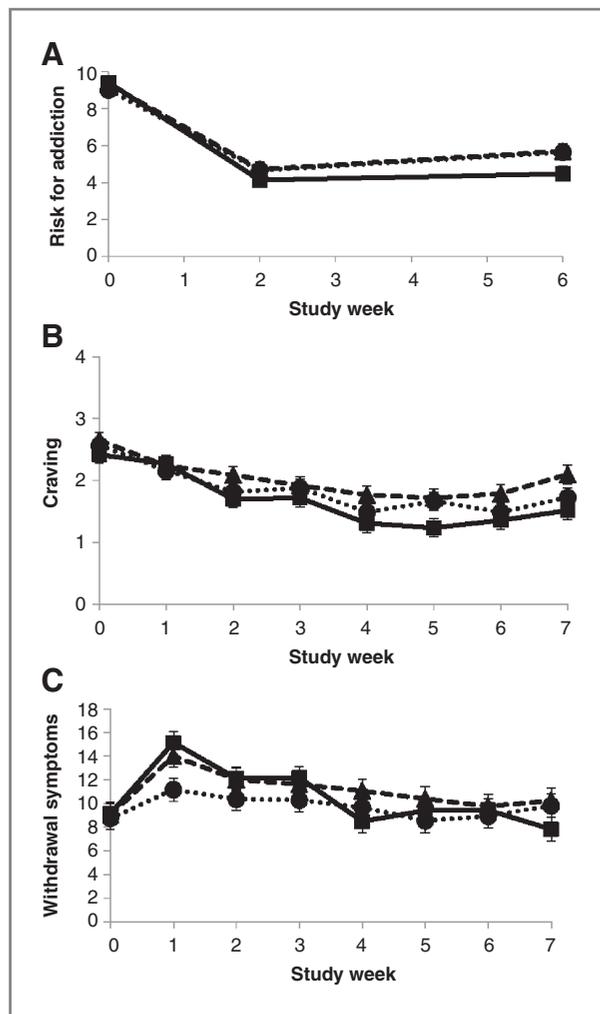
Figure 3. LS mean (±SE) of perceived health risk addiction score at baseline, week 2 and week 6 (A). LS mean (±SE) of craving and withdrawal symptoms (B and C) at baseline through week 7. Triangle represents VLNC cigarette alone; square represents nicotine patch alone; circle represents VLNC + NP.

cigarettes alone. As expected, both nicotine patch and VLNC + nicotine patch conditions resulted in higher levels of cotinine and TNE than VLNC alone condition. All treatment conditions showed a significant reduction in biomarkers of exposure compared with baseline. The combination condition also resulted in lower severity of withdrawal when switching from usual brand cigarettes to the assigned products (although only nearly significant different from VLNC alone), with no difference between nicotine patch and VLNC only conditions. Cessation from product use led to an increase in craving with no differences across groups and a change in withdrawal symptoms. Although not significantly different across groups, withdrawal symptom severity decreased with patch but increased in the conditions that used VLNC. Most importantly, the amount of usual brand smoking was lowest in the combination condition during the product assignment

period. Thus, in general, the combination approach performed significantly better on many outcome variables than the conditions alone. However, exploratory analysis showed that after the product assignment, higher rates of usual brand cigarette abstinence in the combination condition were not sustained and no differences were observed across conditions.

The results from the VLNC cigarettes observed in this study are concordant with findings from a prior study that we conducted in which a VLNC cigarette (Quest 3) was compared with a higher reduced nicotine content cigarette and with the nicotine lozenge (6). The VLNC cigarettes led to reduced rates of smoking and reduced levels of CO, cotinine, and total NNAL levels compared with baseline and no greater withdrawal symptoms or differences in treatment outcome compared with nicotine lozenge alone.

Five other studies have examined the use of the nicotine patch in combination with the VLNC cigarettes. In a 10-day laboratory study conducted by Donny and Jones (20), subjects ($N = 68$) were randomly assigned one of 4 conditions: (i) placebo patch plus nicotine-containing cigarettes (Quest 1, 0.6 mg nicotine yield, 0/NC); (ii) placebo patch plus VLNC cigarettes (Quest 3, 0.05 mg nicotine yield, 0/VLNC); (iii), 7 mg nicotine patch plus VLNC cigarettes (7/VLNC), and (iv) 21 mg nicotine patch plus VLNC (21/VLNC). Consistent with our findings, subjects assigned to the 7 or 21/VLNC compared with 0/VLNC showed a greater decrease in the number of VLNC cigarettes smoked. These subjects also showed a greater decrease in total volume of VLNC cigarette smoke inhaled. Similarly, there was a trend toward participants in the 21/VLNC to show a greater decrease in CO relative to baseline and significantly less increase in CO boost after smoking the VLNC cigarette than participants in the 0/VLNC. Finally, greater withdrawal symptom relief was observed in the 7 or 21/VLNC compared with the 0/VLNC during a required abstinence period when subjects used their assigned products in a laboratory setting.

In another small, pilot treatment study ($N = 16–17$ in each condition), 2 weeks before quit date, smokers were assigned to nicotine or placebo patch in each of 3 cigarette conditions containing different levels of nicotine (21). Relevant to our study, during 2 weeks before the quitting date, subjects assigned to VLNC cigarettes (0.08 mg nicotine) reported smoking 3 usual brand cigarettes in nicotine patch condition as opposed to 46 usual brand cigarettes in the placebo condition. In addition, in the VLNC condition, nicotine patch compared with placebo patch treatment was associated with a lower number of total cigarettes smoked per day but no differences were observed in CO levels, or effects on craving or withdrawal symptoms.

Walker and colleagues in 2012 (3) conducted a large randomized controlled trial to determine the effects of VLNC cigarettes (Quest 3) plus usual Quitline care (NRT and behavioral support) versus Quitline care alone on smoking abstinence. Smokers randomized to VLNC

Table 3. Continuous (since week 6) and point-prevalence (past 1 week) posttreatment abstinence rates

CO- and cotinine-verified continuous abstinence

| | Treatments | | | | | | |
| | VLNC cigarette ($n = 79$) | | Nicotine patch ($n = 80$) | | VLNC + NP ($n = 76$) | | |
Week	# abstinent	%	# abstinent	%	# abstinent	%	P
12	11	13.9	11	13.8	8	10.5	0.776
24	9	11.4	10	12.5	6	7.9	0.625
36	8	10.1	8	10.0	6	7.9	0.867

CO-verified point prevalence abstinence

| | Treatments | | | | | | |
| | VLNC cigarette ($n = 79$) | | Nicotine patch ($n = 80$) | | Combination ($n = 76$) | | |
Week	# abstinent	%	# abstinent	%	# abstinent	%	P
12	21	26.6	24	30.0	22	29.0	0.888
16	21	26.6	20	25.0	23	30.3	0.752
24	18	22.8	17	21.3	16	21.1	0.959
36	15	19.0	19	23.8	16	21.1	0.763

CO- and cotinine-verified point prevalence abstinence

| | Treatments | | | | | | |
| | VLNC cigarette ($n = 79$) | | Nicotine patch ($n = 80$) | | Combination ($n = 76$) | | |
Week	# abstinent	%	# abstinent	%	# abstinent	%	P
12	19	24.1	19	23.8	18	23.7	0.998
24	15	19.0	16	20.0	13	17.1	0.896
36	14	17.7	15	18.8	15	19.7	0.950

NP, nicotine patch.

cigarettes were instructed to use these cigarettes whenever they had an urge to smoke for up to 6 weeks after their quit date. The results showed that more subjects withdrew in the usual care group compared with the group assigned the VLNC cigarettes (32 vs. 11 at 6 months). Furthermore, the group assigned the VLNC cigarettes had higher 7-day point prevalence abstinence rate at the 6 month follow-up compared with usual care (33% vs. 28%, Relative Risk (RR) = 1.18, 95% CI 1.01–1.39) and higher continuous abstinence rates (23% vs. 15%, RR = 1.50, 95% CI 1.20–1.87). Median time to relapse in the group assigned VLNC cigarettes was 2 months compared with 2 weeks in the usual care. Thus, unlike the results from the current study, the combination approach seemed to improve long-term cessation rate.

Two other studies were conducted that did not directly examine the effects of adding nicotine patch to VLNC cigarettes, but showed the principle that providing nicotine through the use of nicotine patch but dissociating the direct delivery of nicotine with cigarette smoking through the use of VLNC cigarettes may ease craving (22) or facilitate cessation (23) compared with continued use of higher level nicotine containing cigarettes before cessation (24).

The results from our studies and other studies may have implications both for treatment and for a potential national policy measure. For treatment, studies support the notion that targeting both the sensory aspects of smoking and nicotine addiction through the slow delivery nicotine (thereby dissociating smoking with the delivery of nicotine) provides greater withdrawal relief and may minimize use of usual brand cigarettes while on treatment or, based on the findings of other studies, at follow-up.

A national policy measure to reduce the levels of nicotine to nonaddicting levels will undoubtedly require access to different pharmacotherapies for tobacco cessation. The availability of the pharmacotherapies may not only reduce the discomfort associated with the reduced nicotine content cigarettes but may lead to substantial reductions in cigarette smoking and possibly to eventual cessation of all products.

There are several limitations to this study. First, no placebo patch was provided so it is unclear as to whether smoking reduction was due to subject concern about smoking and using the patch at the same time. On the other hand, this study represents more naturalistic comparisons of the effects combining both products.

Furthermore, Donny and Jones (20) incorporated placebo patch in their study and observed similar results. Second, the short duration on product may have led to insignificant differences in treatment outcome during follow-up. In addition, for a clinical trial, the sample size was quite small. Third, VLNC cigarettes were switched in the middle of the study because the manufacturer had stopped making the initial cigarettes that were used. Therefore, the level of nicotine was increased. However, prior studies showed that significant reduction in cigarette smoking occur when cigarettes reach less than 0.1 mg nicotine yield (5, 25). In addition, when analyzing only those who received the Xodus product, the results were similar. Finally, we were unable to verify self-reported abstinence from usual cigarettes during product assignment. However, the patterns of biomarkers of exposures across the groups did not indicate that one group was more likely to report inaccurate data than another group.

In summary, the results from this study suggest that combining nicotine replacements with VLNC cigarettes may improve any acute effects resulting from switching to VLNC compared with VLNC alone and lead to a greater reduction in withdrawal discomfort or use of usual brand cigarette during treatment compared with the nicotine patch alone.

Authors' Contributions

Conception and design: D.K. Hatsukami
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.K. Hatsukami, R.I. Vogel, S.E. Murphy, S.S. Hecht, A.M. Joseph, S.S. Allen
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References

1. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med 1994;331:123–5.
2. Hatsukami D, Perkins KA, Lesage MG, Ashley DL, Henningfield JE, Benowitz NL, et al. Nicotine reduction revisited: science and future directions. Tob Control 2010;19:e1–10.
3. Walker N, Howe C, Bullen C, Grigg M, Glover M, McRobbie H, et al. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. Addiction 2012;107:1857–67.
4. Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P III. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. Cancer Epidemiol Biomarkers Prev 2007;16:2479–85.
5. Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, et al. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. Cancer Epidemiol Biomarkers Prev 2012;21:761–9.
6. Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction 2010;105:343–55.
7. Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. Nicotine Tob Res 2006;8:309–13.
8. Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. Treating tobacco use and dependence: 2008 update. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2008.
9. Jacob P III, Byrd GD. Use of chromatographic and mass spectrometric techniques for the determination of nicotine and its metabolites. In: Gorrod JW, Jacob P III, editors. Analytical determination of nicotine and related compounds and their metabolites. Amsterdam: Elsevier; 1999. p. 191–224.
10. Hecht SS, Carmella SG, Murphy SE. Effects of watercress consumption on urinary metabolites of nicotine in smokers. Cancer Epidemiol Biomarkers Prev 1999;8:907–13.
11. Carmella SG, Han S, Fristad A, Yang Y, Hecht SS. Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. Cancer Epidemiol Biomarkers Prev 2003;12:1257–61.
12. Hatsukami D, McBride C, Pirie P, Hellerstedt W, Lando H. Effects of nicotine gum on prevalence and severity of withdrawal in female cigarette smokers. J Subst Abuse 1991;3:427–40.
13. Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal: a replication and extension. Arch Gen Psychiatry 1991;48:52–9.
14. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986;43:289–94.
15. Hatsukami D, Anton D, Keenan R, Callies A. Smokeless tobacco abstinence effects and nicotine gum dose. Psychopharmacology (Berl) 1992;106:60–6.
16. Hatsukami D, Huber M, Callies A. Physical dependence on nicotine gum: effect of duration on use. Psychopharmacology 1993;111:449–56.
17. Hatsukami D, Gust SW, Keenan RM. Physiologic and subjective changes from smokeless tobacco withdrawal. Clin Pharmacol Ther 1987;41:103–7.
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br J Addict 1991;86:1119–27.
19. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.

20. Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. Drug Alcohol Depend 2009;104: 23–33.

21. Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. Nicotine Tob Res 2006;8:89–101.

22. Rezaishiraz H, Hyland A, Mahoney MC, O'Connor RJ, Cummings KM. Treating smokers before the quit date: can nicotine patches and denicotinized cigarettes reduce cravings? Nicotine Tob Res 2007;9:1139–46.

23. Becker KM, Rose JE, Albino AP. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. Nicotine Tob Res 2008;10: 1139–48.

24. Rose JE. Nicotine and nonnicotine factors in cigarette addiction. Psychopharmacology (Berl) 2006;184:274–85.

25. Benowitz N. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. Clin Pharmacol Ther 2008;83:531–41.

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