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# Sex differences in response to reduced nicotine content cigarettes

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## HIGHLIGHTS

- Sex differences in response to VLNC cigarettes +/− nicotine patch were observed.
- Males report better responses when adding the nicotine patch to VLNC.
- Addition of nicotine patch to VLNC cigarettes does not affect female responses.

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## ABSTRACT

*Background:* When switching from usual brand cigarettes, very low nicotine content (VLNC) cigarettes lead to a reduction in the number of cigarettes smoked, toxicant exposure, withdrawal symptoms and dependence. One area that has been relatively unexplored is what factors might moderate the effects of VLNC cigarettes. This exploratory analysis focuses on sex differences in responses to VLNC cigarettes and nicotine replacement therapy.
*Methods:* An exploratory secondary analysis of a randomized trial of 235 participants (58% female, mean age 47 years) comparing a) 0.05–0.09 mg nicotine yield cigarettes; b) 21 mg nicotine patch and 3) 0.05–0.09 nicotine yield cigarettes with 21 mg nicotine patch was conducted. We focused on sex differences in product use, and impact of products on withdrawal response from usual brand cigarettes and abstinence by randomized group.
*Results:* The combination of VLNC cigarettes and nicotine patch was more effective in reducing use of VLNC cigarettes and withdrawal symptoms among males than females, whereas females were equally responsive to VLNC cigarettes with and without the nicotine patch. Females were more likely to quit smoking than males when assigned to either of the conditions that incorporated the VLNC cigarettes; however, males were more likely to quit smoking in the nicotine patch alone condition than females.
*Conclusion:* Sex of the smoker may be an important determinant for effects of VLNC cigarettes and nicotine patch. Future large randomized trials to confirm these results are needed.



## 1. Introduction

Reduced nicotine content cigarettes have been considered a possible adjunctive treatment for smoking cessation (Hatsukami et al., 2010, 2013; Walker et al., 2012) and as a policy measure to reduce the negative public health impact of smoking in the United States (Benowitz & Henningfield, 1994, 2013; Hatsukami et al., 2010). Switching to smoking very low nicotine content (VLNC) cigarettes from usual brand cigarettes has been shown to reduce the number of cigarettes smoked, toxicant exposure, withdrawal symptoms and dependence (Benowitz et al., 2007, 2012; Hatsukami et al., 2010, 2013). Furthermore, smoking VLNC cigarettes may facilitate abstinence (Hatsukami et al., 2010, 2013; Walker et al., 2012), particularly when used alongside nicotine replacement therapies (NRT) (Walker et al., 2012).

One area remaining relatively unexplored is what factors might moderate the effects of VLNC cigarettes. As described in a prior review, these factors include sex, race/ethnicity, age, social economic status, extent (light and heavy) and pattern (intermittent and daily) of smoking, level of dependence, extent of nicotine exposure, rate of nicotine

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metabolism, psychiatric co-morbidities including substance abuse, and possibly genotype (CYP2A6 genetic polymorphism, α3β4α5 nicotinic receptor genotype) (Hatsukami, Benowitz, Donny, Henningfield, & Zeller, 2013). It is important to explore moderating factors in order to predict the impact of VLNC cigarettes as an intervention or public health strategy in key populations.

A review by Perkins (2009), describes studies that demonstrate females have reduced sensitivity to nicotine reinforcement and reward. Females, compared to males, show less differential self-administration of nicotine versus placebo when administered via nasal spray, less choice of nicotine spray over placebo, and less response to pre-treatment with nicotine (especially at lower doses of nicotine). Perkins, Jacobs, Sanders, and Caggiula (2002) administered subjects' own brand cigarettes and cigarettes with a nicotine yield of 0.1 mg in a double-blind manner to participants. They observed a dose by sex interaction where females experienced less difference in subjective responses (e.g., satisfaction, perceived nicotine content, similarity to own brand) between the two different yield cigarettes compared to males. Furthermore, when given the opportunity to work for additional puffs on a cigarette, no differences were observed between the two yield cigarettes for females while males earned more puffs on the higher doses cigarette.

Studies have also shown that females appear more sensitive to visual, olfactory and taste cues than males (Evans, Blank, Sams, Weaver, & Eissenberg, 2006; Perkins et al., 2001, 2002). Females also report greater behavioral dependence (Bohadana, Nilsson, Rasmussen, & Martinet, 2003; Perkins, 2009) and less nicotine dependence with cigarettes. The greater importance of cues is also found in the animal literature, in which cues presented concurrently with nicotine infusion led to greater self-administration in females compared to males (Chaudhri et al., 2005; Donny et al., 2000).

The aim of this exploratory secondary analysis is to examine sex differences in responses to VLNC cigarettes and NRT. This is important as VLNC cigarettes may improve smoking cessation outcomes among females in a way that current NRTs have not been as successful. To explore this issue, we analyzed data from a recently completed randomized trial of smokers assigned to 0.05–0.09 mg nicotine yield cigarettes, nicotine patch, or combination of both products for a period of 6 weeks by sex (Hatsukami et al., 2013).

## 2. Materials and methods

### 2.1. Subjects and study design

Methods for this study have been previously published (Hatsukami et al., 2013). The Institutional Review Board at the University of Minnesota approved this study and all participants provided consent. Briefly, we conducted a randomized-trial at two sites in Minnesota (Minneapolis, Duluth), recruiting smokers who were interested in quitting smoking through advertisements. The advertisements included a description of the study as a novel approach to quitting smoking by using a new tobacco product to aid in the transition of becoming smoke free. Participants were screened over the telephone to determine if they met the following eligibility criteria: 1) smoking 10–40 cigarettes per day for the past year; 2) demonstrating stable medical and mental health and; 3) no contraindications for medicinal nicotine products; and 4) not using any other tobacco products besides cigarettes. Females could not be pregnant or breast feeding. Subjects who were eligible attended an orientation meeting during which the study was described, informed consent was obtained, and a more thorough screening was conducted.

Those who met the eligibility criteria were assigned to one of three treatment conditions: 1) VLNC cigarettes only (0.05 mg nicotine yield [Quest 3] or 0.09 mg nicotine yield [Xodus] cigarettes; yields changed because Quest 3 went off the market during the study); 2) 21 mg nicotine patch only and 3) combination condition (VLNC cigarettes and nicotine patch) for a period of 6 weeks. Smokers in the cigarette conditions were informed that they should smoke the study cigarettes exclusively and ad libitum. Smokers assigned to the nicotine patch were provided instructions described in the medication insert and asked to only use the nicotine patch as the medicinal nicotine product. At the end of the 6-week product use period, participants were asked to discontinue all product use and provided behavioral treatment for an additional 6 weeks. The study coordinators provided the behavioral treatment counseling and were not blinded to the subject's treatment assignment. Follow-up occurred at 36 weeks from the initiation of the study.

### 2.2. Measures

The primary outcome measures for this exploratory analysis included number of VLNC and usual brand cigarettes smoked during treatment, biomarkers of tobacco exposure, withdrawal symptoms, and subjective measures of product satisfaction. Use of usual brand cigarettes and study products were assessed with daily diaries and confirmed at clinic visits. Biomarkers of tobacco exposure measures included a) alveolar carbon monoxide (CO); b) urinary total nicotine equivalents (TNE; (Hecht et al., 1999; Jacob & Byrd, 1999)); c) urinary total cotinine, a metabolite of nicotine ((Jacob & Byrd, 1999)); and d) urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; (Carmella, Han, Fristad, Yang, & Hecht, 2003)). Subjective measures included the Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986, 1998) and modified Cigarette Evaluation Scale (Cappelleri et al., 2007; Westman, Levin, & Rose, 1992). Demographics and smoking history data were collected, including the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Participants were seen weekly for two baseline visits and eight treatment visits with additional treatment visits at weeks 10 and 12 and follow-up visits at weeks 16, 24 and 36. All measurements were ascertained at baseline. Number of cigarettes smoked and CO were assessed at each time point, TNE and NNAL at week 6, and total cotinine at weeks 2, 6, 12, 16, 24 and 36. The Minnesota Nicotine Withdrawal Scale was completed from baseline through week 7, the Cigarette Evaluation Scale and was completed from baseline through week 6.

Additionally, an exploratory analysis of abstinence was performed. Participants were classified as being continuously abstinent for each visit (yes/no) if from the time of treatment initiation to that visit they did not have even 1 puff of usual brand cigarettes (during the study product treatment period weeks 1–6) and any tobacco after the treatment period. Biochemically verified (CO < 6 ppm and cotinine <35 ng/mL) continuous abstinence rates during weeks 12, 24, and 36 were calculated. Drop-outs were considered to have slipped at the date of their last follow-up visit.

### 2.3. Statistical analysis

Demographic data and smoking history were summarized using descriptive statistics. Baseline sex differences were determined using Pearson's $\chi^2$ tests or Fisher's exact tests for categorical data and t-tests or Kruskal–Wallis tests for continuous data.

As in the main study, we conducted an intention-to-treat analysis. Continuous outcomes with repeated measures were analyzed using linear mixed models (Verbeke & Molenberghs, 2009) including fixed treatment, visit, sex, treatment by visit, sex by treatment, sex by visit, and sex by treatment by visit interaction effects, and a random effect for subject. Analyses of product use, biomarkers, and abstinence also included a fixed effect of cigarettes per day at baseline as differences were expected and observed between sexes at baseline. Biomarkers were adjusted for creatinine and analyzed on the natural log scale to ensure normality. Differences in abstinence rates were analyzed using logistic regression models, including treatment, sex, and sex by treatment interaction effects. Statistically significant effects ($p < 0.05$) were probed using

post-hoc t-tests. The p-value for each post-hoc test was adjusted for multiple comparisons within each outcome using a Bonferroni correction.

Although a sub-group exploratory analysis by sex was planned a priori, this study was not designed to have appropriate power to detect interactions by sex. Note that while the sample sizes in each treatment group for the primary comparisons were 76–90, once this was additionally split by gender these numbers were reduced 32–47 participants in each treatment group. Therefore, analyses were also conducted stratified by sex to explore patterns for those without statistically significant sex by treatment or sex by treatment by visit interaction effects. These results should be interpreted cautiously as this is a secondary analysis with a relatively small sample size for this purpose.

Nicotine craving and withdrawal were determined using the Minnesota Nicotine Withdrawal Scale, with craving as a single item and withdrawal a summary score of the remaining 14 items. In addition to examining the outcomes across the 6 study visits, analyses were conducted to focus on expected peak changes in craving and withdrawal symptoms, specifically when switching from usual brand cigarettes to the assigned products (baseline to week 1) and when coming off the study products (week 6 to week 7).

## 3. Results

Of the 235 subjects who consented and participated in the study, 136 (57.9%) were female. Baseline demographics were similar between males and females with the exception of marital status, with more of the males being currently married ($p = 0.007$), and number of cigarettes smoked per day, with males smoking more cigarettes on average than females ($p = 0.005$, Table 1). There did not appear to be any sex differences in nicotine dependence, number of quit attempts or motivation to quit. Males and females statistically significantly differed in their exposure to TNE ($p = 0.005$) and total NNAL ($p = 0.027$) at baseline, though total cotinine was not statistically significant ($p = 0.183$). Females had higher values for all three biomarkers.

### 3.1. Product use

Stratified analyses are presented for study cigarette use because the sex by treatment ($p = 0.186$) and sex by treatment by visit ($p = 0.981$) interactions were not statistically significant. For both sexes (Fig. 1), there were statistically significant treatment, visit, and treatment by visit effects on study cigarette use during the treatment period (all $p \leq 0.001$). When focusing on the VLNC cigarette only and combination groups, males assigned to the combination group smoked statistically significantly less study cigarettes during treatment than those in the VLNC cigarette only group ($p < 0.05$ each week). Among females, there was no statistically significant difference between these two groups overall or at any visit ($p > 0.20$ each week).

When analyzing use of usual brand cigarettes during the treatment period, there was not a statistically significant sex by treatment interaction effect ($p = 0.879$), however, there were statistically significant sex by visit ($p = 0.024$) and sex by treatment by visit interactions ($p = 0.018$). In particular, males in the nicotine patch group smoked the most usual brand cigarettes following randomization but tapered over the treatment period whereas the number of usual brand cigarettes smoked remained stable in both the VLNC cigarette and combination groups. In contrast, females increased smoking of usual brand cigarettes slightly over the treatment period after an initial decrease in use, regardless of treatment assignment. Patterns of usual brand cigarette use during the 6-week period *after* the study product assignment period did not differ by sex (data not shown).

### 3.2. Biomarkers of exposure

The sex by treatment interactions were not statistically significant for TNE ($p = 0.856$), total cotinine ($p = 0.666$), or total NNAL ($p = 0.792$) at the end of the study product treatment period. Furthermore, stratified analyses of TNE, total cotinine, and total NNAL were not suggestive of sex differences.

There were no statistically significant sex by treatment ($p = 0.190$) or sex by treatment by visit interaction effects ($p = 0.411$) for CO levels

**Table 1**
Baseline demographics and smoking history of subjects by sex. In instances where data are missing, the total number of subjects used in calculating values is fewer than the 235 randomized to treatment.

| | Overall | | Males | | Females | | p-value |
|---|---|---|---|---|---|---|---|
| Age (years) | 235 | 47.0 ± 11.7 | 99 | 48.1 ± 11.0 | 136 | 46.1 ± 12.1 | 0.216 |
| Non-Hispanic Whites | 191 | 82.0% | 78 | 79.6 | 113 | 83.7 | 0.420 |
| Education | | | | | | | 0.920 |
| 8th grade or less | 2 | 0.9% | 0 | 0.0 | 2 | 1.5 | |
| Some high school | 6 | 2.6% | 2 | 2.0 | 4 | 3.0 | |
| High school graduate | 53 | 22.8% | 23 | 23.5 | 30 | 22.2 | |
| Some college/2-year | 132 | 56.7% | 55 | 56.1 | 77 | 57.0 | |
| College graduate/4-year | 32 | 13.7% | 15 | 15.3 | 17 | 12.6 | |
| Graduate degree | 8 | 3.4% | 3 | 3.1 | 5 | 3.7 | |
| Marital status | | | | | | | 0.007 |
| Never married | 63 | 26.8% | 22 | 22.2 | 41 | 30.2 | |
| Currently married | 91 | 38.7% | 50 | 50.5 | 41 | 30.2 | |
| Currently not married | 81 | 34.5% | 27 | 27.3 | 54 | 39.7 | |
| Cigarettes per day | 235 | 18.9 ± 7.2 | 99 | 21.0 ± 9.7 | 136 | 18.4 ± 6.8 | 0.005 |
| Years of smoking | 234 | 29.1 ± 12.0 | 98 | 30.7 ± 11.7 | 136 | 28.0 ± 12.1 | 0.092 |
| Age smoking first cigarette (yrs) | 235 | 14.6 ± 3.9 | 99 | 14.2 ± 3.5 | 136 | 14.9 ± 4.1 | 0.154 |
| Age regular smoker (yrs) | 234 | 17.9 ± 4.6 | 98 | 17.6 ± 4.5 | 136 | 18.2 ± 4.6 | 0.320 |
| Number of quit attempts | | | | | | | 0.296 |
| 1–2 | 51 | 23.5% | 18 | 20.7 | 33 | 25.4 | |
| 3–5 | 86 | 39.6% | 31 | 35.6 | 55 | 42.3 | |
| 6–10 | 49 | 22.6% | 26 | 29.9 | 23 | 17.7 | |
| 11–20 | 24 | 11.1% | 10 | 11.5 | 14 | 10.8 | |
| 20+ | 7 | 3.2% | 2 | 2.3 | 5 | 3.9 | |
| Motivation to quit (0–10) | 224 | 8.5 ± 1.4 | 95 | 8.5 ± 1.5 | 129 | 8.5 ± 1.4 | 0.940 |
| Fagerstrom Test for Nicotine Dependence | 228 | 5.4 ± 1.9 | 96 | 5.4 ± 2.0 | 132 | 5.3 ± 1.9 | 0.719 |
| Total TNE (nmol/mg creatinine) | 172 | 59.9 ± 28.3 | 70 | 51.7 ± 22.5 | 102 | 65.5 ± 30.5 | 0.005 |
| Total cotinine (nmol/mg creatinine) | 172 | 20.2 ± 10.6 | 70 | 18.7 ± 9.5 | 102 | 21.3 ± 11.1 | 0.183 |
| Total NNAL (pmol/mg creatinine) | 170 | 1.4 ± 0.9 | 70 | 1.3 ± 0.8 | 100 | 1.5 ± 0.9 | 0.027 |

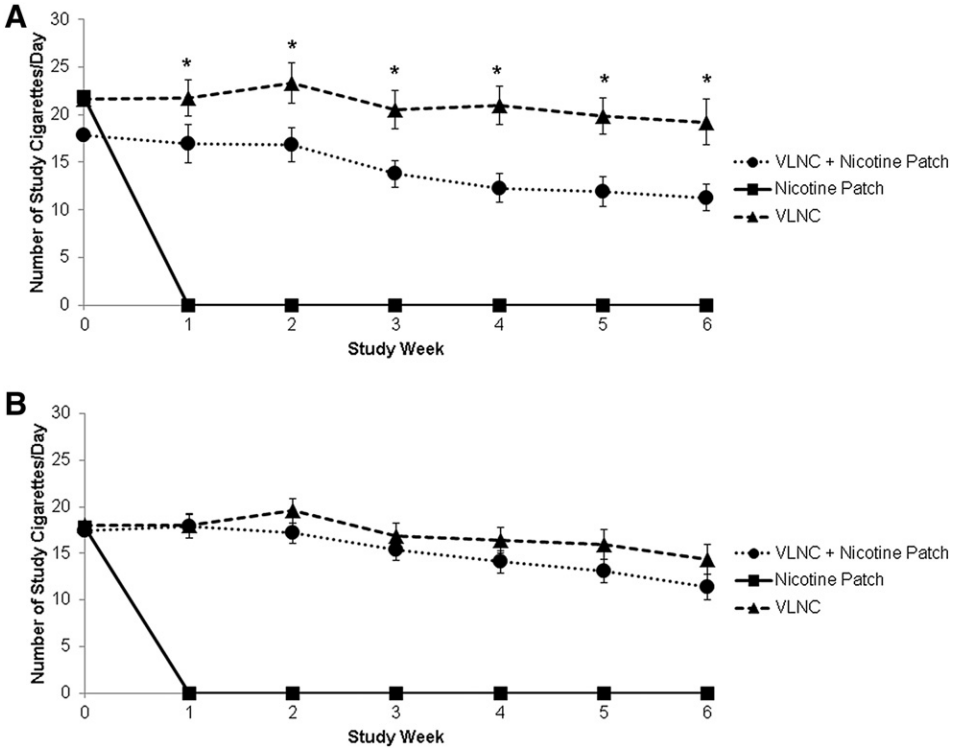


**Fig. 1.** Least squares mean (±SE) of number of study cigarettes smoked per day for males (panel A) and females (panel B). Visit 0 data represent usual brand cigarette use. Triangle represents very low nicotine content (VLNC) cigarette alone; square represents nicotine patch alone; circle represents combination group. An asterisk (*) above a visit indicates a statistically significant difference between the VLNC alone and combination groups for that visit.

over the treatment period. Stratified analyses, however, were suggestive of differences within each sex (Fig. 2). Among males, there were statistically significant treatment ($p < 0.001$) and visit ($p = 0.010$) effects, however, there was no treatment by visit interaction ($p = 0.568$). Males assigned to the VLNC only group had the highest CO levels, followed by the combination and nicotine patch only groups; this

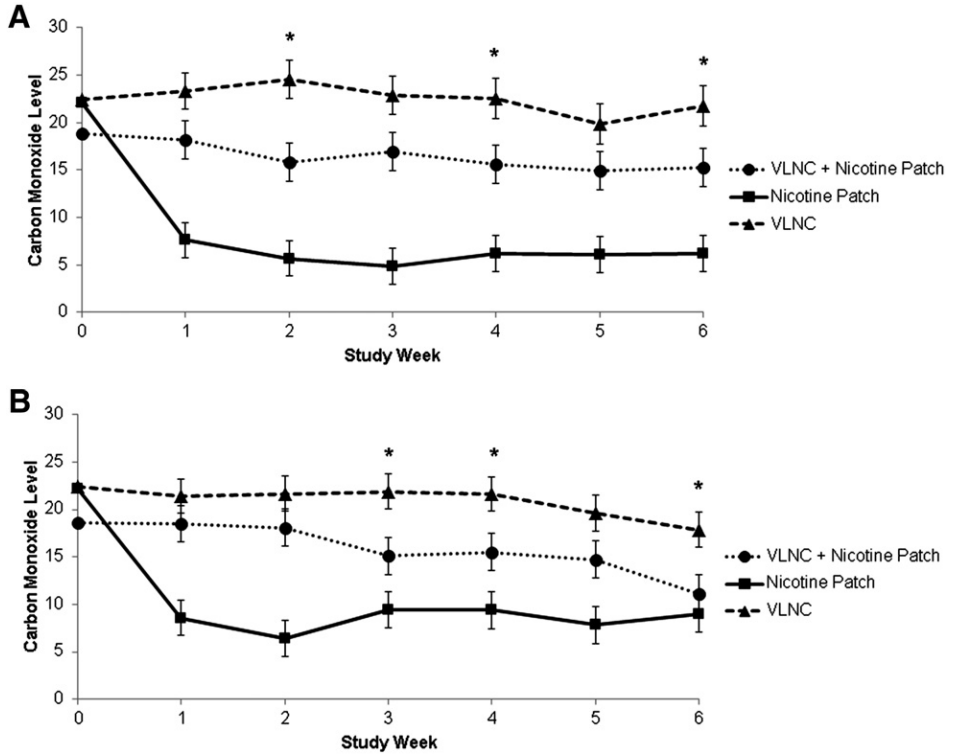


**Fig. 2.** Least squares mean (±SE) of exhaled carbon monoxide for males (panel A) and females (panel B). Triangle represents very low nicotine content (VLNC) cigarette alone; square represents nicotine patch alone; circle represents combination group. An asterisk (*) above a visit indicates a statistically significant difference between the VLNC alone and combination groups for that visit.

pattern did not change over time. In females, there were statistically significant treatment ($p < 0.001$), visit ($p = 0.005$) and treatment by visit interaction ($p = 0.025$) effects. In particular, CO levels in females assigned to the combination group decreased over time while the others remained fairly constant after the initial decrease following randomization.

### 3.3. Subject responses to products

#### 3.3.1. Nicotine craving and withdrawal

Patterns of nicotine craving and withdrawal symptoms for males and females in each treatment condition during the 6-week study product treatment period and week 7 are illustrated in Figs. 3A–D. For the purposes of this analysis, we focused on changes surrounding product switching.

The sex by treatment interaction was statistically significant for nicotine craving ($p = 0.022$) and borderline statistically significant for withdrawal ($p = 0.084$) when switching from usual brand cigarettes to the assigned study products (baseline to week 1). In males, there did not appear to be a change in craving upon cessation of usual brand cigarettes and starting study products, whereas there was a statistically significant decrease in craving in females. For withdrawal, males had increased withdrawal scores, with those assigned combination group reporting lower withdrawal symptoms than those in the nicotine patch group alone. In females, there was also an increase in withdrawal symptoms but they did not differ by treatment assignment.

The sex by treatment interaction upon cessation of the study products (week 6 to week 7) was not statistically significant for craving ($p = 0.585$) or withdrawal ($p = 0.762$). Stratified analyses indicate a statistically significant increase in craving both in males ($p = 0.016$) and females ($p < 0.0001$), however, the differences by treatment group were not quite statistically significant ($p = 0.110$ and $p = 0.095$, respectively). Similarly, there were statistically significant differences in withdrawal symptoms upon cessation of the study products for males ($p < 0.0001$) and females ($p < 0.0001$), however, these did not differ significantly by treatment group in either sex.

#### 3.3.2. Product satisfaction

There was a statistically significant sex by treatment interaction for reported satisfaction with the VLNC cigarette among those assigned to the VLNC or combination groups ($p = 0.009$; Fig. 4). Females assigned to the VLNC cigarette group reported greater satisfaction with the VLNC cigarettes alone than the combination group whereas males assigned to the combination group reported greater satisfaction than with the VLNC cigarettes alone. There were no statistical or apparent sex differences in other dimensions of product evaluation, including psychological reward, aversive symptoms, and sensations in mouth (data not shown).

### 3.4. Abstinence

The treatment effect on biochemically verified continuous abstinence from cigarettes at weeks 12, 24, and 36 differed statistically significantly by sex (Table 2). In particular, at week 12, males assigned to the nicotine patch exhibited the greatest reported abstinence (20.6%), followed by the combination (6.1%) and VLNC cigarette (3.1%) groups. In contrast, females assigned to the VLNC cigarette group exhibited the greatest reported continuous abstinence (21.3%), followed by the combination (14.0%) and nicotine patch (8.7%) groups. The odds ratio for abstinence in men for VLNC cigarette vs. combination was about half (0.49, 95% CI: 0.22–1.07) of that in women, whereas the odds ratio for abstinence in men for nicotine patch vs. combination was more than twice (2.32, 95% CI: 1.24–4.35) than that in women. The

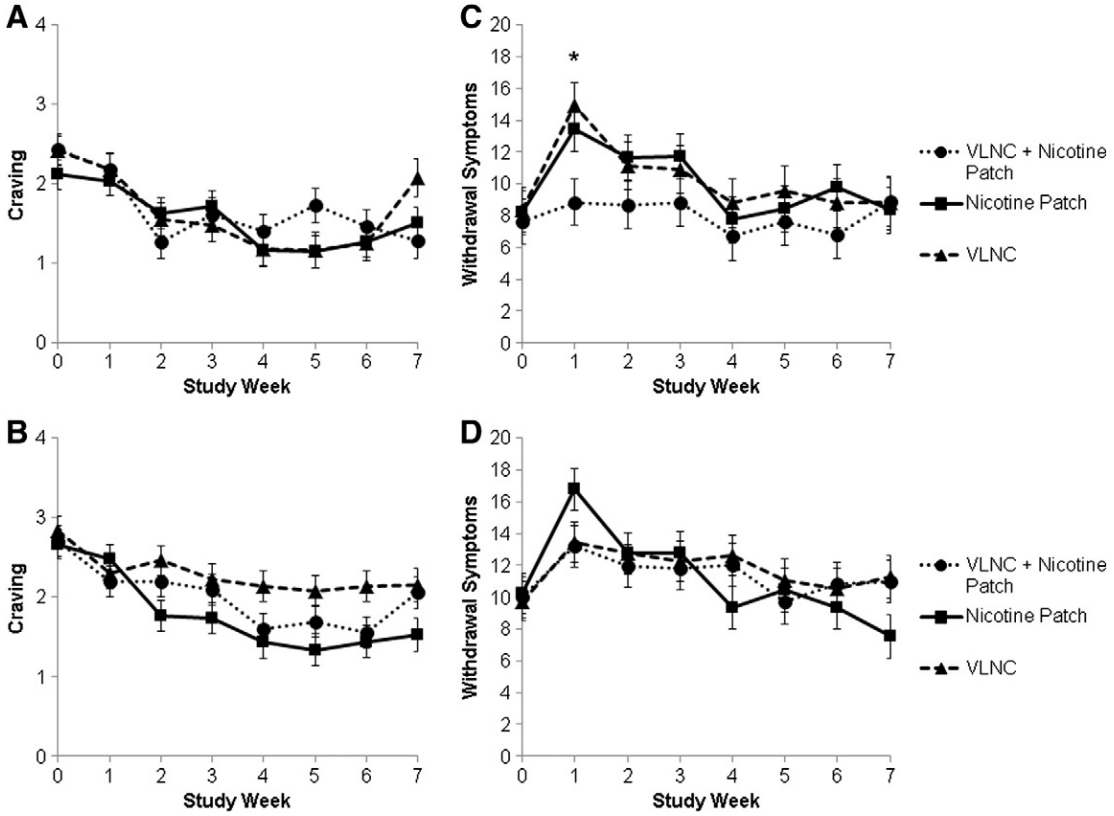


**Fig. 3.** Least squares mean (±SE) of craving and withdrawal symptoms for males (panels A and C) and females (panels B and D) at baseline through week 7. Triangle represents very low nicotine content (VLNC) cigarette alone; square represents nicotine patch alone; circle represents combination group. An asterisk (*) above a visit indicates a statistically significant difference between the VLNC alone and combination groups for that visit.

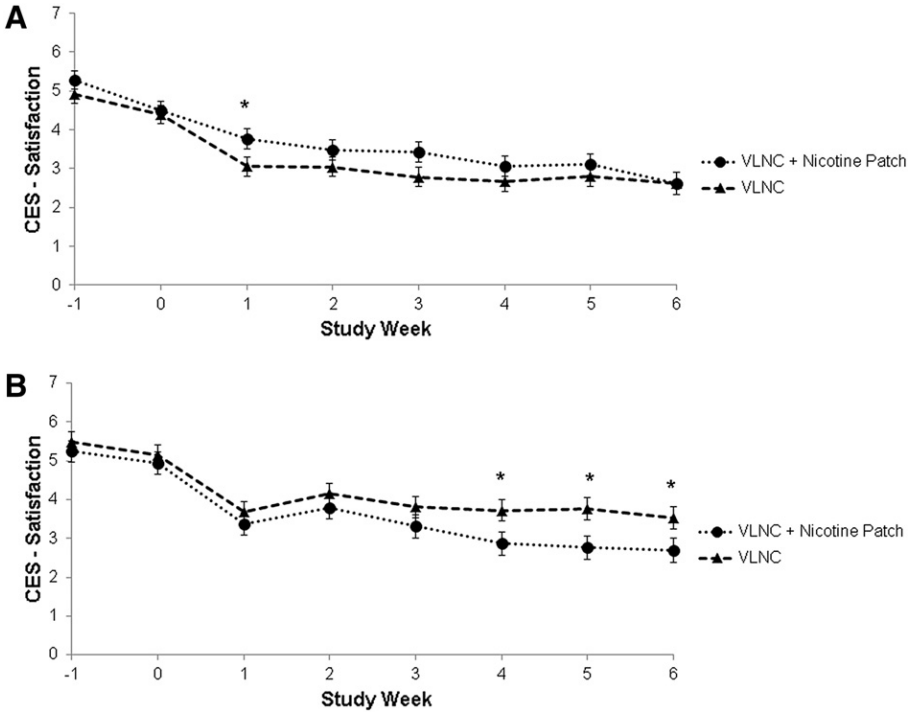


**Fig. 4.** Least squares mean (±SE) of satisfaction with VLNC cigarettes for males (panel A) and females (panel B). The screening (−1) and baseline (0) visits represent satisfaction with usual brand cigarettes. Triangle represents very low nicotine content (VLNC) cigarette alone; circle represents combination group. An asterisk (*) above a visit indicates a statistically significant difference between the VLNC alone and combination groups for that visit.

same pattern of findings was supported at weeks 24 and 36, however, the effects were less robust than week 12.

## 4. Discussion

Most results of this exploratory analysis are consistent with the prior studies that show that males are more responsive to nicotine than females and females to the sensory aspects of smoking (Perkins, 2009). In this study, in general males benefited most (in terms of number of VLNC cigarettes smoked and withdrawal) when nicotine patch was added to VLNC cigarettes whereas females assigned to the VLNC cigarettes had no additional benefit with the addition of the nicotine patch. For instance, while male smokers assigned to the combination group smoked fewer study cigarettes than those who are assigned to the VLNC cigarettes alone, there were no treatment effects on study cigarette use among female smokers. Despite this, CO levels were lower in the combination group compared to the VLNC cigarettes only group in both sexes. It is possible that while the addition of the nicotine patch may not impact the number of cigarettes smoked for females, it may affect the manner by which the cigarettes are smoked (e.g., number and volume of puffs).

When looking at subjective responses such as withdrawal symptoms and product satisfaction, males also appeared to be more responsive to the addition of the nicotine patch to the VLNC cigarettes than females. For instance, males experienced greater suppression of withdrawal when assigned to the combination group than when assigned to the VLNC cigarettes alone. In contrast, those in the combination group did not further reduce withdrawal among females compared to those in the VLNC cigarettes only group. Similarly, satisfaction with the VLNC cigarettes was augmented when combined with the nicotine patch in males, but for females, this combination was associated with reduced satisfaction compared to the VLNC cigarette alone condition.

Contrary to these results, males assigned to the combination group had lower abstinence rates compared to the nicotine patch only group; this result requires further exploration and confirmation with a larger sample size. It is possible that because men are more sensitive to nicotine, they may find a product with very little nicotine more unpleasant or less satisfying. Although adding the nicotine patch reduced withdrawal and enhanced satisfaction with the cigarettes, these effects may not be sufficient enough to find these cigarettes useful in cessation for males. In contrast, we found that in females, who are more sensitive to sensory aspects of smoking, adding the patch led to less satisfaction

**Table 2**
Continuous abstinence rates by sex.

| CO and cotinine verified continuous abstinence | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Males | | | | | | Females | | | | | | p-value * |
| | VLNC (n = 32) | | Nicotine patch (n = 34) | | Combination (n = 33) | | VLNC (n = 47) | | Nicotine patch (n = 46) | | Combination (n = 43) | | |
| | # abstinent | % | # abstinent | % | # abstinent | % | # abstinent | % | # abstinent | % | # abstinent | % | |
| 12 | 1 | 3.1 | 7 | 20.6 | 2 | 6.1 | 10 | 21.3 | 4 | 8.7 | 6 | 14.0 | 0.029 |
| 24 | 1 | 3.1 | 6 | 17.7 | 1 | 3.0 | 8 | 17.0 | 4 | 8.7 | 5 | 11.6 | 0.059 |
| 36 | 1 | 3.1 | 5 | 14.7 | 1 | 3.0 | 7 | 14.9 | 3 | 6.5 | 5 | 11.6 | 0.078 |

* P-value for treatment by sex interaction.

with the VLNC cigarettes, though we are unable to speculate as to why this was the case.

In general, these findings are consistent with prior studies. NRTs have led to a greater suppression in withdrawal (Hatsukami, Skoog, Allen, & Bliss, 1995; Wetter et al., 1999) and craving (Killen, Fortmann, Newman, & Varady, 1990; Perkins et al., 2006) symptoms in males versus females, despite being shown to be effective in promoting smoking cessation for both sexes (Shiffman, Sweeney, & Dresler, 2005). On the other hand, prior studies show a VNLC cigarette provided abstinence-induced craving relief in females but not in males (Barrett, 2010).

Males in our study tended to have higher abstinence rates with the nicotine patch than females, which is similar to the results observed in a meta-analysis of clinical trials (Perkins & Scott, 2008), with the calculated interaction odds ratio of 2.32 comparing nicotine patch to VLNC cigarette being similar to their calculated interaction odds ratio of 1.40 comparing nicotine patch to placebo patch in men versus women. Females tended to have higher abstinence rates in the VLNC cigarette alone condition than males, demonstrating that providing the sensory aspects of smoking during a quit attempt be more beneficial to females than males. Becker et al. (2008) found that use of VLNC cigarettes plus NRT compared to conventional cigarettes plus subsequent use of NRT was more effective in promoting 4 week continuous abstinence rates in females but not males. Another study showed that females had higher abstinence rates using the nicotine inhaler, which provides the behavioral and sensory aspects of smoking, than when using nicotine gum; but males fared better with the nicotine gum than the inhaler (West et al., 2001). However, in another study, males experienced higher cessation rates using nicotine inhalers with or without nicotine patches than females (Bohadana et al., 2003). A recent study suggests these differences in smoking cessation between males and females using NRT may be because nicotine affects a key neuroreceptor (e.g. β2 AChR) differently in the two sexes (Cosgrove et al., 2012).

The major limitation of this study was the sample size and the post-hoc nature of the analysis. The sample size reported in this study is similar to others reporting such secondary analyses; the meta-analysis provided by Perkins and Scott (2008) provides the most compelling data on sex differences to date and required use of 14 individual studies ranging in sample sizes from 112 to 1686 each, none of which reported statistically significant sex interactions on their own. It is important to note that given the sample size and number of outcomes explored, some of the observed differences may have occurred due to chance variation, although the results are consistent with findings from prior studies. Additionally, we did not address measured baseline differences by sex beyond cigarettes per day or potential unmeasured differences such as psychological co-morbidities. These baseline differences may partly explain the associations found in this analysis. Finally, the behavioral cessation counseling was not conducted by counselors blind to the subject's treatment condition, therefore introducing a possible source of bias.

Despite these limitations, our findings underscore the importance of examining sex differences. A large randomized trial is necessary to confirm these results.

## 5. Conclusions

When considering the overall pattern of findings across the outcomes, this exploratory secondary data analysis suggests gender differences in the responses to NRT and VLNC cigarettes. In particular, among females, the most desirable outcomes were achieved with VLNC cigarettes. For none of the outcomes did NRT alone outperform treatment with VLNC cigarettes and in most cases the addition of nicotine patch did not augment the effects of VLNC cigarettes alone. In contrast, among males, NRT was a necessary component for the most positive treatment outcomes for each significant outcome and in some cases (i.e., biomarkers, abstinence) NRT alone outperformed conditions with VLNC cigarettes. While these findings need to be replicated, they are consistent with the literature suggesting differential sensitivity to the rewarding effects of nicotine and smoking behavior among men and women. It is possible that nicotine replacement is a key component to successful cessation among men while replacement of smoking cues is critical for treatment among women.

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**Contributors**

Author Hatsukami designed the study and outlined and edited the manuscript. Authors Hatsukami and al'Absi provided oversight at the study sites. Authors Hertsgaard and Moua collected data and Allen monitored the participants for medical safety. Author Hertsgaard performed initial literature review. Author Vogel undertook the statistical analysis and wrote the first draft of the manuscript. Authors Dermody and Luo provided significant contributions to analysis methods. All authors contributed to and approved the final manuscript.

**Conflict of interest**

Dorothy Hatsukami received funding from Nabi Biopharmaceuticals to conduct a trial on the nicotine vaccine. No other conflicts of interests.

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