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Effects of Very Low Nicotine Content Cigarettes on Smoking Behavior and Biomarkers of Exposure in Menthol and Non-menthol Smokers

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Abstract

Introduction: Because 30% of cigarettes sold in the United States are characterized as menthol cigarettes, it is important to understand how menthol preference may affect the impact of a nicotine reduction policy.

Methods: In a recent trial, non-treatment-seeking smokers were randomly assigned to receive very low nicotine cigarettes (VLNC; 0.4 mg nicotine/g tobacco) or normal nicotine cigarettes (NNC; 15.5 mg/g) for 20 weeks. On the basis of preference, participants received menthol or non-menthol cigarettes. We conducted multivariable regression analyses to examine whether menthol preference moderated the effects of nicotine content on cigarettes per day (CPD), breath carbon monoxide (CO), urinary total nicotine equivalents (TNE), urinary 2-cyanoethylmercapturic acid (CEMA), and abstinence.

Results: At baseline, menthol smokers (n = 346) reported smoking fewer CPD (14.9 vs. 19.2) and had lower TNE (52.8 vs. 71.6 nmol/mg) and CO (17.7 vs. 20.5 ppm) levels than non-menthol smokers (n = 406; ps < .05). At week 20, significant interactions indicated that menthol smokers had smaller treatment effects than non-menthol smokers for CPD (–6.4 vs. –9.3), TNE (ratio of geometric means, 0.22 vs. 0.10) and CEMA (ratio, 0.56 vs. 0.37; ps < .05), and trended toward a smaller treatment effect for CO (–4.5 vs. –7.3 ppm; p = .06). Odds ratios for abstinence at week 20 were 1.88 (95%

confidence interval [CI] = 0.8 to 4.4) for menthol and 9.11 (95% CI = 3.3 to 25.2) for non-menthol VLNC smokers (p = .02) relative to the NNC condition.

Conclusions: Although menthol smokers experienced reductions in smoking, toxicant exposure, and increases in quitting when using VLNC cigarettes, the magnitude of change was smaller than that observed for non-menthol smokers.

Implications: Results of this analysis suggest that smokers of menthol cigarettes may respond to a nicotine reduction policy with smaller reductions in smoking rates and toxicant exposure than would smokers of non-menthol cigarettes.

Introduction

The Food and Drug Administration (FDA) recently announced a tobacco control framework focused on reducing the addictiveness of cigarettes as a means of reducing the public health burden of smoking in the United States.[1] A mandated reduction in the nicotine content of all commercially available cigarettes to a minimally addictive level is the foundation of this framework. Data from several clinical trials provide evidence to support a nicotine reduction policy as a viable public health approach, with studies reporting reductions in cigarette smoking, toxicant exposure, and nicotine dependence, as well as increases in spontaneous quit attempts.[2–9] A policy simulation estimated that approximately 5 million smokers would quit within the first year of an FDA-mandated low-nicotine product standard for cigarettes and would likely result in 16 million fewer people initiating smoking and 2.8 million fewer tobacco-related deaths by 2060.[10] Given these findings, the FDA issued an Advance Notice of Proposed Rulemaking in March 2018 regarding a low-nicotine product standard for cigarettes, signaling its interest in moving forward with this regulatory action.

Cigarettes containing menthol as a characterizing flavor comprise approximately 30% of the US cigarette market share and are disproportionately used by racial/ethnic minorities, sexual and gender minorities, adolescents, young adults, and individuals with psychiatric disorders.[11–18] In 2017, over 34 million people in the United States smoked cigarettes.[19] Thus, a low-nicotine product standard for cigarettes would affect upward of 10 million menthol cigarette smokers. Yet, previous trials of very low nicotine content (VLNC) cigarettes have not consistently or extensively reported trial outcomes by menthol smoking status, so relatively little is known about how menthol flavoring will affect the effects of cigarette nicotine reduction. Preclinical research indicates that menthol flavoring contributes to nicotine reinforcement and self-administration.[20–23] A laboratory assessment of research cigarettes varying in nicotine content reported that menthol smokers required higher doses for discriminating nicotine in cigarettes compared to non-menthol smokers, suggesting that they are less sensitive to differences in nicotine content.[24] Together, these studies suggest that menthol smokers could potentially be less sensitive to the effects of cigarette nicotine content on smoking behavior. However, no clinical trials have directly examined this question.

Recently, a 20-week trial was conducted to determine the optimal approach for implementing a low-nicotine product standard for cigarettes (ie, immediate vs. gradual reduction in nicotine content).[9] Results of that study indicated that immediate reduction led to significantly greater decreases in biomarkers of smoke exposure compared to the gradual reduction and control conditions. The purpose of the current secondary analysis is to compare outcomes from that trial by menthol smoking status among participants assigned to the immediate reduction condition (VLNC) and the normal nicotine content (NNC) control condition. We excluded participants in the gradual reduction condition because biomarkers of smoke exposure were not decreased in this condition relative to the control condition in the clinical trial.[9]

Because menthol flavoring may contribute to cigarette reinforcement,[20–23] we hypothesized that the effect of VLNC cigarettes on smoking behavior and biomarkers of nicotine and toxicant exposure would be smaller in menthol smokers than non-menthol smokers. Furthermore, since menthol cigarette smoking is associated with poorer cessation outcomes,[25–28] we hypothesized that the effect of VLNC cigarettes on the odds of being abstinent at the end of the trial and the odds of having at least one cigarette-free day during the trial would be lower in the participants using menthol cigarettes than in participants using non-menthol cigarettes.

Methods

Participants

Adult smokers were recruited from 10 sites across the United States. To be eligible, participants had to smoke at least five cigarettes per day (CPD), on average, for the past year, have an expired breath carbon monoxide (CO) level more than 8 ppm (or urinary cotinine level > 1000 ng/ml), and report no intention to quit smoking in the next 30 days. Exclusion criteria included recent alcohol use (breath alcohol level > 0.02% at screening), a positive urine toxicology test (excluding cannabis), unstable medical or psychiatric conditions, pregnancy or lactation, use of other tobacco products more than 9 days in the past 30, exclusive use of roll-your-own cigarettes, and prior use of low nicotine content cigarettes during the past 3 years. Study procedures were approved by institutional review boards at all 10 sites, reviewed by the FDA's Center for Tobacco Products (CTP) and the National Institute on Drug Abuse (NIDA), and monitored by an external data safety and monitoring board. All participants provided written informed consent before enrollment.

Study Design

After completing a 2-week baseline phase during which participants smoked their usual brand of cigarettes, participants were randomly assigned to a NNC control condition (15.5 mg nicotine/g tobacco), an immediate reduction condition (0.4 mg nicotine/g tobacco research cigarettes; VLNC), or a gradual reduction condition (15.5, 11.7, 5.2, 2.4, and 0.4 mg nicotine/g tobacco; 4 weeks per dose). The research cigarettes were provided by NIDA and have been described in detail elsewhere.[6] For the present analyses, we excluded participants in the gradual reduction condition. Menthol smoking status

was determined by asking participants if they preferred to receive menthol or non-menthol research cigarettes for the duration of the 20-week intervention.

Participants attended weekly visits between randomization and week 4 and then bi-weekly visits from weeks 6–20. At each visit, participants received 14- or 28-day supplies of their assigned research cigarettes, free of charge, to allow for any potential changes in smoking behavior or to accommodate missed visits. Staff instructed the participants to use only their assigned research cigarettes if they smoked but emphasized honest self-report about their use of non-study cigarettes. Participants reported—separately—the number of study and non-study cigarettes smoked each day using a telephone interactive voice response system. During the visits, participants completed questionnaires about their tobacco use and subjective responses to the cigarettes and provided biological samples (eg, expired breath CO samples; first void urine samples at each monthly visit) to assess biomarkers of nicotine and toxicant exposure. To increase compliance with smoking only the study cigarettes, participants were incentivized with a bonus at the end of the trial. Participants in the VLNC condition received the bonus if their urinary total nicotine equivalents (TNE) levels were ≤ 12 nmol/ml, indicating they were mostly compliant with smoking the study cigarettes. All participants in the NNC condition received the bonus at the end of the trial regardless of their urinary nicotine levels. Additional study details have been previously reported.[9]

Measures

To assess differences between cigarette conditions in smoking behavior during the trial, we examined the following outcomes: (1) mean total CPD (ie, sum of study and non-study cigarettes) at week 20; (2) CO-verified abstinence at week 20 (CO ≤ 5 ppm; for the intent-to-treat analysis missing samples were imputed as non-abstinent [CO > 5 ppm], whereas the per-protocol analysis included only participants with CO samples at week 20); (3) any cigarette-free days during the 20-week trial (yes/no); and (4) mean number of cigarette-free days during the 20-week trial.

To measure differences between cigarette conditions on biomarkers of nicotine and toxicant exposure, we examined the following outcomes: (1) expired breath CO at week 20; (2) urinary TNE at week 20; (3) urinary 3-hydroxypropylmercapturic acid (3-HPMA) and 2-cyanoethylmercapturic acid (CEMA), metabolites of the volatile organic compounds acrolein and acrylonitrile, at week 20; (4) urinary phenanthrene tetraol (PheT), an indicator of exposure to polycyclic aromatic hydrocarbons, at week 20; and (5) urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite for the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), at week 20.

To assess differences between cigarette conditions on changes in behavioral and subjective responses to the research cigarettes, we examined the following outcomes at week 20: (1) study attrition; (2) Minnesota Nicotine Withdrawal Scale (MNWS)[29]; (3) Questionnaire on Smoking Urges - 10 (QSU),[30] Factors 1 and 2; (4) modified Cigarette Evaluation Questionnaire (mCEQ)[31]—Satisfaction, Psychological Reward, Aversion, Craving Reduction and Enjoyment in the Respiratory Tract subscales; and (5) study cigarette compliance, which included only participants in the VLNC condition. A urinary TNE criterion of ≤ 6.41 nmol/ml classified participants as being compliant with smoking only the VLNC cigarettes.[32]

Statistical Analyses

For this secondary analysis, we used linear, logistic, and negative binomial regression to examine whether menthol smoking status moderated the effect of cigarette nicotine content on trial outcomes at week 20 in the immediate reduction and normal nicotine control conditions. Our primary interest was to compare treatment effects (ie, differences between participants randomized to the VLNC and NNC groups) by cigarette flavor (menthol vs. non-menthol), which was completed by including a nicotine content by cigarette flavor interaction term in all regression models. Regression models also included the corresponding baseline values of the outcome measure (when available), study site, age, race, employment status, educational attainment, smoking duration, Fagerström Test for Nicotine Dependence level, serum nicotine metabolite ratio, and baseline values of urine TNE, CPD, and expired CO as covariates. Race, educational attainment, employment status, CPD, smoking duration, CO, and TNE were included in the model because they were significantly associated with menthol smoking status at baseline. Other covariates were included in the model to be consistent with the adjusted analysis reported in the primary manuscript.[9]

Because menthol smoking status differed by race, we also conducted exploratory analyses within the subset of participants identifying as white to minimize potential confounding between race and menthol smoking status on responses to VLNC cigarettes. Given the small sample size of black non-menthol smokers (n = 22), it was not feasible to examine the effects of cigarette nicotine condition in black menthol versus non-menthol smokers. A previous smoking cessation trial reported poorer cessation outcomes among white menthol smokers relative to white non-menthol smokers,[25] so we hypothesized that the VLNC cigarette treatment effects would be smaller among white menthol smokers relative to white non-menthol smokers. For these exploratory analyses, we applied the same statistical approaches described earlier but removed race and added gender as a covariate in the regression models because gender differed significantly at baseline by menthol smoking status among white participants.

TNE, 3-HPMA, CEMA, PheT, and NNAL were natural log-transformed and analyzed using linear regression; CO-verified abstinence, study attrition, and any cigarette-free days were analyzed using logistic regression; number of cigarette-free days was analyzed using negative binomial regression; and all other endpoints were analyzed using linear regression on the original scale. Tests were considered significant at $\alpha = 0.05$, two-tailed. Because the purpose of this study was to explore the potential negative impact of menthol flavoring on nicotine reduction outcomes and the parent trial was not originally powered to test this interaction, we prioritized avoiding Type II error over Type I error. Therefore, we did not correct for multiple statistical comparisons. Analyses were conducted using R statistical software, version 3.3.0.[33]

Results

Baseline Characteristics by Menthol Smoking Status

Table 1 shows demographic and baseline smoking characteristics in the menthol smokers (n = 346) and non-menthol smokers (n = 406). At baseline, menthol smokers reported smoking fewer CPD (14.9 vs. 19.2; $p < .01$) and had lower TNE (52.8 vs. 71.6 nmol/mg creatinine; $p < .01$) and CO levels (17.7 vs. 20.5 ppm; $p < .01$) than non-menthol smokers. There were significant differences in menthol

Table 1. Baseline Demographics for All Participants by Menthol Smoking Status and Treatment Condition

Characteristics	Menthol smokers	Non-menthol smokers	*p* Value	Menthol: control	Menthol: immediate	*p* Value	Non-menthol: control	Non-menthol: immediate	*p* Value
Sample size	346	406		115	231		134	272	
Age, mean (SD), years	44.6 (12.9)	46 (14.4)	.14	44.1 (12.5)	44.8 (13.1)	.61	45.8 (14.1)	46.1 (14.5)	.81
Female, No. (%)	162 (47)	177 (44)	.42	50 (43)	112 (48)	.44	58 (43)	119 (44)	1
Race, No. (%)			<.001			.68			.99
White	120 (35)	342 (86)		36 (32)	84 (37)		113 (86)	229 (85)	
Black	195 (58)	22 (6)		66 (59)	129 (57)		7 (5)	15 (6)	
Other	24 (7)	36 (9)		9 (8)	15 (7)		12 (9)	24 (9)	
Hispanic, No. (%)	23 (7)	19 (5)	.31	11 (10)	12 (5)	.19	4 (3)	15 (6)	.38
Education, No. (%)			<.001			.81			.25
< High school	40 (12)	23 (6)		15 (13)	25 (11)		5 (4)	18 (7)	
High school	123 (36)	110 (27)		41 (36)	82 (35)		42 (31)	68 (25)	
> High school	183 (53)	273 (67)		59 (51)	124 (54)		87 (65)	186 (68)	
Employment			.02			.74			.11
Employed (full/part-time)	133 (38)	183 (45)		43 (37)	90 (39)		56 (42)	127 (47)	
Unemployed	92 (27)	77 (19)		32 (28)	60 (26)		29 (22)	48 (18)	
Disability	41 (12)	35 (9)		11 (10)	30 (13)		17 (13)	18 (7)	
Other	80 (23)	111 (27)		29 (25)	51 (22)		32 (24)	79 (29)	
Cigarettes per day, mean (SD)	14.9 (7.1)	19.2 (9.3)	<.001	15.3 (7.6)	14.8 (6.8)	.49	18.6 (8.5)	19.5 (9.6)	.31
Years of regular smoking, mean (SD)	25.5 (13.1)	28.5 (14.5)	<.001	25.1 (12.3)	25.8 (13.5)	.66	28.1 (14.5)	28.7 (14.5)	.67
CO, ppm, mean (SD)	17.7 (8.7)	20.5 (9.7)	<.001	18 (8.7)	17.6 (8.7)	.66	20.5 (9.9)	20.5 (9.6)	.96
TNE, nmol/mg creatinine, median (range)	52.8 (0.2, 258.1)	71.6 (3, 497.8)	<.001	51.2 (10.1, 203.7)	53.1 (0.2, 258.1)	.4	69.2 (10.4, 238.8)	72.1 (3, 497.8)	.85
FTND, mean (SD)	5.3 (2.1)	5.4 (2.1)	.65	5.2 (2.1)	5.4 (2.1)	.6	5.1 (2.1)	5.5 (2.1)	.06
Other tobacco products, No. (%)	69 (24)	70 (21)	.42	22 (23)	47 (25)	.85	23 (21)	47 (21)	.97

Baseline demographics for all participants randomized to the immediate nicotine reduction condition (VLNC) or normal nicotine control condition (NNC) by menthol smoking status. Independent *t*-tests were used to compare continuous variables and chi-square tests for independence were used to compare categorical variables. FTND = Fagerström Test for Nicotine Dependence.

smoking status by race such that 90% of black participants smoked menthol cigarettes compared to 26% of white participants ($p < .01$). Menthol smokers were also less likely to be employed (38% vs. 45%; $p = .02$) and had lower educational attainment (> high school education 53% vs. 67%; $p < .01$) than non-menthol smokers. At randomization, participants' research cigarette flavor selections were highly concordant with their self-reported usual brand cigarette flavor. Less than 1% of participants opted to receive research cigarettes that differed in flavor from their usual brand cigarette during the trial. Five participants preferring menthol usual brand cigarettes elected to receive non-menthol research cigarettes whereas four participants preferring non-menthol usual brand cigarettes elected to receive menthol research cigarettes.

Smoking Behavior

VLNC treatment effects at week 20 by menthol smoking status are reported in Table 2, and effects of cigarette nicotine content and menthol smoking status on CPD, percent of participants achieving abstinence, TNE levels, and CEMA levels are shown in Figure 1. At week 20, both menthol and non-menthol smokers in the VLNC condition reported significant reductions in the number of cigarettes smoked per day relative to participants in the NNC condition, as previously reported across both groups.[9] The effect of cigarette nicotine content on the number of cigarettes smoked per day was significantly smaller for participants who smoked menthol cigarettes than for those who smoked non-menthol cigarettes (–6.4 vs. –9.3 CPD, respectively; $p = .04$ for the interaction). The odds ratio for the association between cigarette nicotine content and biochemically verified abstinence at week 20 was significantly smaller for participants who smoked menthol cigarettes than for those who smoked non-menthol cigarettes (intent-to-treat odds ratio = 1.88 vs. 9.11, $p = .02$ for the interaction). Both menthol and non-menthol smokers assigned to VLNC cigarettes were more likely to report at least one cigarette-free day and attained more cigarette-free days during the trial than those assigned to NNC cigarettes (Table 2), and there were no significant interactions between cigarette nicotine content and menthol smoking status on these measures.

Biomarkers of Toxicant Exposure

At week 20, both menthol and non-menthol smokers in the VLNC condition had significant reductions in urinary TNE and CEMA levels relative to participants in the NNC condition, as previously reported across both groups.[9] The treatment effects were significantly smaller for participants who smoked menthol cigarettes compared to participants who smoked non-menthol cigarettes for urinary TNE levels (ratio of geometric means; 0.22 vs. 0.1, $p = .01$ for the interaction) and urinary CEMA levels (ratio of geometric means; 0.56 vs. 0.37, $p = .05$ for the interaction). In addition, there was a trend for a smaller treatment effect on expired breath CO exposure among participants who smoked menthol cigarettes relative to those who smoked non-menthol cigarettes (–4.5 vs. –7.3 ppm, $p = .06$ for the interaction). Levels of 3-HPMA, PheT, and NNAL were lower in the VLNC condition than the NNC condition across menthol status conditions, but there were no significant interactions between cigarette nicotine content and menthol smoking status for these outcomes (Table 2).

Behavioral and Subjective Responses to the Research Cigarettes

Study completion rates, QSU craving levels, and positive subjective ratings of the study cigarettes were lower in the VLNC condition than the NNC condition across menthol status conditions at week 20 (Table 2), but there were no significant interactions between cigarette nicotine content and menthol smoking status for these outcomes. There was a trend for a smaller treatment effect for mCEQ Craving Reduction scores at week 20 among participants who smoked menthol cigarettes (–1.0 vs. –1.6, $p = .09$) but not for the other four mCEQ subscales. In addition, there was no significant interaction for the odds of being biochemically verified as compliant with smoking only the VLNC cigarettes at week 20 (Supplementary Table 1).

Exploratory Analyses Among White Participants

Supplementary Table 2 provides demographic and smoking characteristics for white menthol and non-menthol smokers. At baseline, white menthol smokers ($n = 120$) were younger (42.8 vs. 45.6 years, $p = .02$), more likely to be female (55% vs. 44%, $p = .05$), smoked fewer CPD (17.4 vs. 19.8, $p < .001$), had lower TNE (64.1 vs. 73.3 nmol/mg creatinine, $p = .03$) and had shorter smoking durations (25.4 vs. 29.3 years, $p = .01$) than white non-menthol smokers ($n = 342$). VLNC treatment effects among white participants are reported in Table 3. At week 20, white participants who smoked menthol cigarettes tended to have lower odds of achieving biochemically verified abstinence (OR=1.5 vs. 8.74; $p = .07$ for the interaction) and tended to have smaller mCEQ Craving Reductions scores (–2.4 vs. –5.6; $p = .07$ for the interaction) compared with white participants who smoked non-menthol cigarettes, but these interactions were not significant (Table 3). No other significant interactions effects were observed among white participants at week 20.

Discussion

To date, this is the first VLNC cigarette study to comprehensively report the effects of extended VLNC cigarette use on differences in smoking behavior, toxicant exposure, and subjective cigarette effects by menthol smoking status. Among both menthol and non-menthol smokers, participants assigned to the VLNC condition exhibited less cigarette smoking and toxicant exposure and were more likely to abstain from smoking during the trial, than participants randomized to the NNC condition, as previously reported.[9] We found significant nicotine content by menthol status interactions such that the effect of cigarette nicotine content on the number of cigarettes smoked per day was smaller for menthol smokers than non-menthol smokers. Effects of cigarette condition on biomarkers of nicotine and smoke exposure are consistent with the effects on CPD in that menthol smokers also experienced smaller reductions in nicotine exposure, expired breath CO levels, and levels of urinary CEMA, a biomarker for the toxicant and possible carcinogen, acrylonitrile.[34] However, we did not find significant nicotine content by cigarette flavor interactions for 3-HPMA, PheT, and NNAL, indicating that these risk measures were reduced in all smokers assigned to VLNC cigarettes, notwithstanding their menthol status.

The most striking interaction observed in this study was the difference in the effect of cigarette nicotine content on the likelihood of being abstinent at week 20. The trial enrolled non-treatment-seeking smokers, so this may be a conservative estimate of spontaneous quitting at the population level. Yet, the interaction between nicotine content and menthol smoking status on abstinence rates indicates that the effects of cigarette nicotine reduction on smoking cessation may be greater in non-menthol smokers than menthol smokers. These findings align with prior smoking cessation studies that reported poorer cessation outcomes for menthol smokers compared to non-menthol smokers.[25–27,35]

Table 2. Treatment Effect on Outcomes at Week 20 for All Participants by Menthol Smoking Status

	Interaction tests		Menthol smokers				Non-menthol smokers			
	Unadjusted model[1]	Adjusted model[2]	Unadjusted model[1]		Adjusted model[2]		Unadjusted model[1]		Adjusted model[2]	
Outcome	*p* Value	*p* Value	Treatment effect	*p* Value	Treatment effect	*p* Value	Treatment effect	*p* Value	Treatment effect	*p* Value
Total CPD	.037	.043	−6.1 (−8.1, −4)	<.001	−6.4 (−8.5, −4.3)	<.001	−9 (−10.9, −7.2)	<.001	−9.3 (−11.2, −7.5)	<.001
Any cigarette-free days	.818	.903	1.91 (1.17, 3.12)	.01	2.02 (1.18, 3.49)	.011	1.76 (1.09, 2.85)	.022	2.12 (1.24, 3.62)	.006
Mean cigarette-free days	.13	.417	2.41 (1.17, 4.95)	.017	4.48 (2.2, 9.1)	<.001	5.15 (2.64, 10.05)	<.001	6.71 (3.45, 13.04)	<.001
CO-verified abstinence (per-protocol)	.057	.009	2.51 (1.18, 5.34)	.017	2.71 (1.1, 6.7)	.031	8.18 (3.15, 21.19)	<.001	17.64 (6.02, 51.68)	<.001
CO-verified abstinence (intent-to-treat)*	.065	.02	1.87 (0.89, 3.94)	.097	1.88 (0.8, 4.43)	.148	5.81 (2.26, 14.94)	<.001	9.11 (3.3, 25.18)	<.001
CO	.19	.058	−4.8 (−6.9, −2.6)	<.001	−4.5 (−6.6, −2.3)	<.001	−6.7 (−8.7, −4.8)	<.001	−7.3 (−9.3, −5.3)	<.001
TNE	.011	.011	0.22 (0.14, 0.35)	<.001	0.22 (0.14, 0.35)	<.001	0.1 (0.07, 0.15)	<.001	0.1 (0.07, 0.15)	<.001
3-HPMA	.237	.151	0.73 (0.6, 0.89)	.002	0.72 (0.59, 0.89)	.002	0.62 (0.51, 0.74)	<.001	0.59 (0.49, 0.71)	<.001
CEMA	.075	.045	0.59 (0.43, 0.8)	.001	0.56 (0.41, 0.76)	<.001	0.4 (0.3, 0.53)	<.001	0.37 (0.28, 0.48)	<.001
PheT	.76	.785	0.78 (0.66, 0.93)	.005	0.75 (0.63, 0.89)	.001	0.75 (0.64,0.88)	<.001	0.73 (0.62, 0.85)	<.001
NNAL	.208	.127	0.49 (0.36, 0.67)	<.001	0.48 (0.35, 0.66)	<.001	0.37 (0.28, 0.5)	<.001	0.34 (0.26, 0.46)	<.001
Completer	.568	.719	0.4 (0.23, 0.71)	.002	0.35 (0.19, 0.66)	.001	0.32 (0.18, 0.57)	<.001	0.3 (0.17, 0.55)	<.001
mCEQ: Aversion	.293	.302	−0.1 (−0.3, 0.1)	.518	−0.1 (−0.3, 0.1)	.52	0.1 (0.1, 0.3)	.393	0.1 (−0.1, 0.3)	.405
mCEQ: Reward	.098	.344	−0.9 (−1.2, −0.7)	<.001	−0.9 (−1.2, −0.6)	<.001	−0.6 (−0.9, 0.4)	<.001	−0.7 (−1, −0.5)	<.001
mCEQ: Satisfaction	.743	.819	−1.6 (−2, −1.3)	<.001	−1.6 (−2, −1.2)	<.001	−1.5 (−1.9, −1.2)	<.001	−1.7 (−2, −1.3)	<.001
mCEQ: Enjoyment	.333	.846	−1.3 (−1.7, −0.9)	<.001	−1.2 (−1.6, −0.8)	<.001	−1 (−1.4, −0.7)	<.001	−1.2 (−1.5, −0.8)	<.001
mCEQ: Craving	.184	.089	−0.9 (−1.4, −0.5)	<.001	−1 (−1.5, −0.5)	<.001	−1.4 (−1.8, −0.9)	<.001	−1.6 (−2, −1.1)	<.001
MNWS	.353	.578	−1 (−2.1, 0.2)	.111	−0.8 (−2, 0.4)	.207	−0.2 (−1.3, 0.9)	.71	−0.3 (−1.4, 0.8)	.568
QSU—Factor 1	.924	.562	−4.6 (−6.3, −2.8)	<.001	−4.7 (−6.5, −2.9)	<.001	−4.7 (−6.3, −3.1)	<.001	−5.4 (−7, −3.8)	<.001
QSU—Factor 2	.165	.371	−2.1 (−3.1, −1.1)	<.001	−2 (−3.1, −1)	<.001	−1.1 (−2, −0.2)	.02	−1.4 (−2.3, −0.5)	.003

Treatment effects—difference in means for CO, total CPD, mCEQ Satisfaction, mCEQ Psychological Reward, mCEQ Aversion, mCEQ Enjoyment in the Respiratory Tract, mCEQ Craving Reduction, MNWS, QSU Factor 1, QSU Factor 2, and number of cigarette-free days; odds ratio for abstinence, attrition, and any cigarette-free days; rate ratio for number of cigarette-free days; ratio of geometric means for all other outcomes.

[1]Adjusts for baseline value of the outcome.

[2]Adjusts for baseline value of the outcome, study site, age, race, educational attainment, employment status, FTND, serum NMR, years of regular smoking, and baseline TNE, CPD, and CO.

*Assumes that missing participants were still smoking (imputed CO level > 5 ppm). FTND = Fagerström Test for Nicotine Dependence.

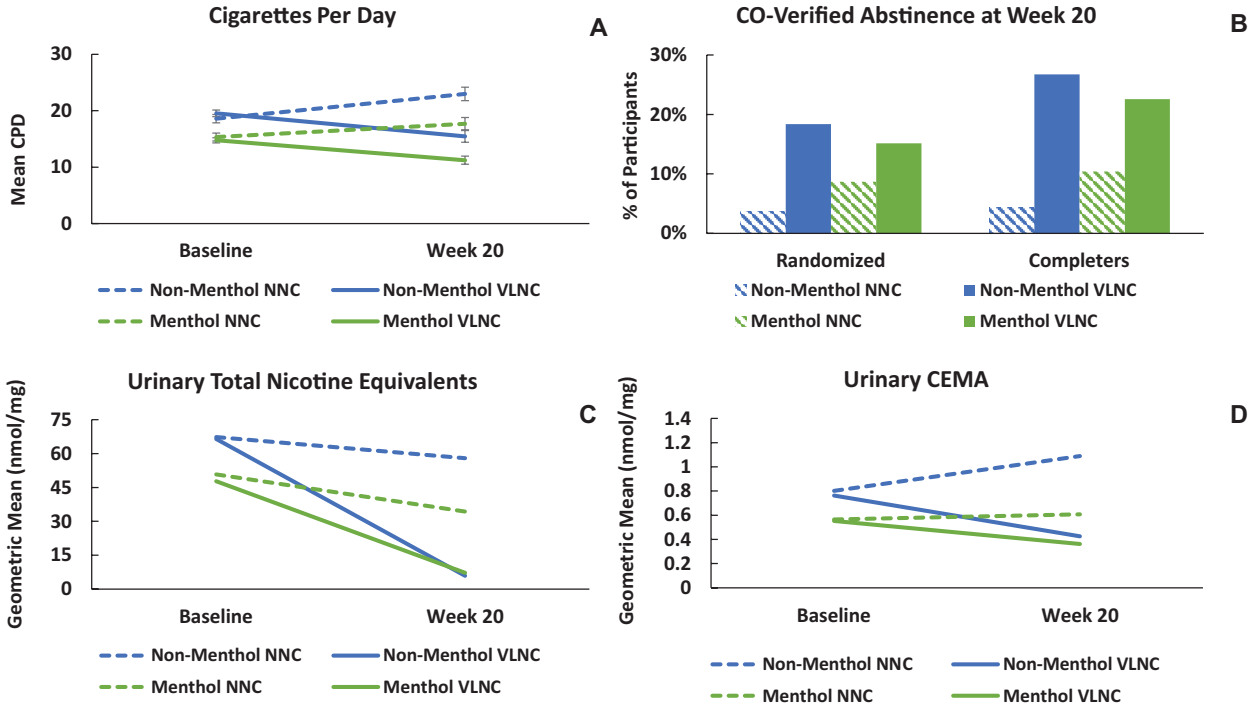

Figure 1. Cigarettes per day, abstinence, and urinary biomarkers of exposure.

In preclinical studies, menthol flavoring has been shown to increase nicotine-self administration.[20–23] Therefore, the smaller treatment effects on CPD observed in this study among menthol smokers could partially be explained by the potential reinforcing effect of menthol flavoring in cigarettes. Alternatively, menthol smokers were lower than non-menthol smokers on most outcomes measured at baseline, so we cannot rule out the possibility that the smaller treatment effects were due, at least in part, to a baseline-dependent effect[36] (ie, that the amount of change in responding following an intervention is dependent on the baseline rate of behavior). For example, although the non-menthol VLNC participants had higher TNE levels than the menthol VLNC participants at baseline, both groups ended up at approximately the same absolute level of nicotine exposure at week 20, suggesting a possible baseline-dependent effect. However, a recent VLNC cigarette trial among non-daily smokers reported significant reductions in the number of cigarettes smoked per day, despite having low baseline smoking rates,[8] indicating a smaller change in menthol smokers may be a pharmacological effect of the intervention rather than a baseline-dependent (ie, non-specific) effect.

Menthol and non-menthol smokers reported similar subjective responses to the research cigarettes during the 20-week trial. We observed a trend toward an interaction between cigarette nicotine content and menthol smoking status on the mCEQ Craving Reduction subscale, a single-item assessment, suggesting that menthol smokers experienced smaller reductions in craving compared to non-menthol smokers. However, no significant interactions were detected for the QSU, a multi-item assessment of cigarette craving, or on the other mCEQ subscales. These findings indicate that VLNC cigarettes were similarly effective at reducing cigarette craving and positive subjective effects of smoking across menthol status conditions, consistent with previous laboratory assessments of VLNC cigarettes comparing subjective smoking outcomes by menthol smoking status.[37,38]

The results of this study should be considered within the context of several limitations. First, menthol smoking status was not randomized. Participants selected whether they wanted to receive menthol or non-menthol research cigarettes for the duration of the trial. Therefore, unknown or unobserved variables that vary by menthol smoking status may have contributed to the differences in treatment effects between menthol and non-menthol smokers observed in this study. Second, menthol smoking status was confounded by race. In the analytic sample (N = 752), only 22 black participants selected non-menthol research cigarettes to smoke during the trial, so the demographic characteristics of the menthol and non-menthol groups differed significantly by race. To address the potential confounding, we first adjusted for race and other related covariates in the regression models. When holding these variables constant, the effects of cigarette nicotine content on smoking behavior and biomarkers of exposure were smaller for menthol smokers than non-menthol smokers. In addition, we conducted separate exploratory analyses of menthol status effects among white participants to remove race as a potential confounder. Although the interactions were no longer statistically significant when the analyses were restricted to white participants, the direction of the effects remained consistent with the overall sample. Furthermore, these findings align with a large cessation trial that reported white menthol smokers had poorer abstinence outcomes compared to white non-menthol smokers.[25] A third limitation is that the trial was not originally powered to detect interaction effects of cigarette nicotine content and menthol smoking status, especially when the sample is restricted to white smokers. Therefore, nonsignificant findings may be partially because of Type II error. Finally, compliance to smoking only VLNC cigarettes during the trial was moderate, with 39% of participants in the VLNC condition achieving the compliance criteria at week 20.[9] Non-compliance in VLNC cigarette trials is problematic because it can lead to underestimations of the treatment effects. However, in this study, there

Table 3. Treatment Effect on Outcomes at Week 20 for White Participants by Menthol Smoking Status

	Interaction tests		Menthol smokers				Non-menthol smokers			
	Unadjusted model[1]	Adjusted model[2]	Unadjusted model[1]		Adjusted model[2]		Unadjusted model[1]		Adjusted model[2]	
Outcome	*p* Value	*p* Value	Treatment effect	*p* Value	Treatment effect	*p* Value	Treatment effect	*p* Value	Treatment effect	*p* Value
Total CPD	.407	.257	−6.7 (−10.7, −2.7)	.001	−6.1 (−10, −2.1)	.003	−8.7 (−10.9, −6.4)	<.001	−8.7 (−10.9, −6.5)	<.001
Any cigarette-free days	.715	.852	2.18 (0.85, 5.59)	.103	2.55 (0.85, 7.65)	.094	1.78 (1.03, 3.07)	.037	2.27 (1.24, 4.16)	.008
Mean cigarette-free days	.669	.283	3.04 (0.76, 12.26)	.117	2.14 (0.54, 8.48)	.278	4.33 (1.93, 9.7)	<.001	5.05 (2.28, 11.19)	<.001
CO-verified abstinence (per-protocol)	.235	.116	2.78 (0.72, 10.74)	.139	3.42 (0.6, 19.34)	.165	7.87 (2.73, 22.73)	<.001	18.19 (5.33, 62.07)	<.001
CO-verified abstinence (intent-to-treat)*	.197	.094	2.01 (0.54, 7.55)	.299	1.94 (0.39, 9.64)	.417	6.12 (2.14, 17.53)	.001	10.38 (3.24, 33.31)	<.001
CO	.475	.339	−4.8 (−8.9, −0.7)	.022	−4.7 (−8.8, −0.7)	.024	−6.5 (−8.7, −4.3)	<.001	−7 (−9.2, −4.8)	<.001
TNE	.98	.673	0.11 (0.05, 0.25)	<.001	0.13 (0.05, 0.29)	<.001	0.11 (0.07, 0.17)	<.001	0.1 (0.06, 0.16)	<.001
3-HPMA	.539	.229	0.76 (0.52, 1.12)	.168	0.83 (0.56, 1.21)	.328	0.67 (0.54, 0.82)	<.001	0.63 (0.51, 0.78)	<.001
CEMA	.596	.306	0.5 (0.29, 0.87)	.015	0.53 (0.31, 0.91)	.021	0.42 (0.31, 0.57)	<.001	0.38 (0.28, 0.51)	<.001
PheT	.453	.596	0.67 (0.5, 0.91)	.01	0.69 (0.51, 0.94)	.018	0.77 (0.65, 0.9)	.002	0.76 (0.64, 0.89)	.001
NNAL	.424	.556	0.3 (0.17, 0.55)	<.001	0.29 (0.16, 0.53)	<.001	0.4 (0.29, 0.55)	<.001	0.36 (0.26, 0.49)	<.001
Completer	.905	.973	0.46 (0.19, 1.14)	.095	0.37 (0.13, 1.03)	.058	0.43 (0.24, 0.79)	.007	0.38 (0.2, 0.73)	.003
mCEQ: Aversion	.641	.655	0.2 (−0.1, 0.6)	.224	0.2 (−0.1, 0.6)	.219	0.1 (−0.1, 0.3)	.202	0.1 (−0.1, 0.3)	.173
mCEQ: Reward	.335	.727	0.9 (−1.4, −0.5)	<.001	−0.8 (−1.3, −0.4)	.001	−0.7 (−0.9, −0.4)	<.001	−0.8 (−1, −0.5)	<.001
mCEQ: Satisfaction	.082	.397	−2.2 (−2.9, −1.6)	<.001	−2 (−2.6, −1.4)	<.001	−1.6 (−1.9, −1.2)	<.001	−1.7 (−2, −1.4)	<.001
mCEQ: Enjoyment	.134	.639	−1.6 (−2.2, −1)	<.001	−1.4 (−2, −0.8)	<.001	−1.1 (−1.4, −0.7)	<.001	−1.2 (−1.6, −0.9)	<.001
mCEQ: Craving	.978	.752	−1.4 (−2.3, −0.5)	.002	−1.4 (−2.3, −0.4)	.004	−1.4 (−1.9, −0.9)	<.001	−1.5 (−2, −1)	<.001
MNWS	.66	.535	0 (−1.9, 1.9)	.984	0.3 (−1.7, 2.3)	.796	−0.5 (−1.5, 0.6)	.377	−0.5 (−1.6, 0.6)	.407
QSU—Factor 1	.186	.073	−4.9 (−6.5, −3.3)	<.001	−2.4 (−5.4, 0.6)	.118	−2.7 (−5.6, 0.3)	.077	−5.6 (−7.2, −3.9)	<.001
QSU—Factor 2	.666	.467	−0.9 (−2.4, 0.6)	.26	−0.9 (−2.4, 0.6)	.251	−1.3 (−2.1, −0.4)	.003	−1.5 (−2.3, −0.7)	<.001

Treatment effects—difference in means for CO, total CPD, mCEQ Satisfaction, mCEQ Psychological Reward, mCEQ Aversion, mCEQ Enjoyment in the Respiratory Tract, mCEQ Craving Reduction, MNWS, QSU Factor 1, QSU Factor 2, and number of cigarette-free days; odds ratio for abstinence, attrition, and any cigarette-free days; rate ratio for number of cigarette-free days; ratio of geometric means for all other outcomes.

[1]Adjusts for baseline value of the outcome.

[2]Adjusts for baseline value of the outcome, study site, age, race, educational attainment, employment status, FTND, serum NMR, years of regular smoking, and baseline TNE, CPD, and CO.

*Assumes that missing participants were still smoking (imputed CO level > 5 ppm). FTND = Fagerström Test for Nicotine Dependence.

was no significant interaction between cigarette nicotine content and menthol smoking status on compliance, bolstering confidence that the differences between menthol and non-menthol smokers in this trial were not because of different rates of VLNC compliance.

Implications for Tobacco Regulation

Additional tobacco control strategies targeting menthol cigarettes could help to augment the public health impact of the proposed nicotine reduction policy. In November 2018, the FDA announced its renewed interest in banning menthol as a characterizing flavor in cigarettes, a policy that has been under consideration for several years.[39] A 2011 report by the FDA's Tobacco Products Scientific Advisory Committee concluded that menthol cigarettes pose a greater public health threat than non-menthol cigarettes, thus banning menthol as a characterizing flavor in cigarettes could improve public health outcomes.[40] Importantly, many menthol smokers report they would quit smoking if menthol cigarettes were no longer commercially available.[41–46] Therefore, a combined policy approach, reducing the nicotine content in cigarettes and banning menthol as a characterizing flavor, has the potential to maximize public health outcomes. A menthol flavor ban for cigarettes could potentially increase motivation to quit and reducing the nicotine content in cigarettes could help to facilitate more successful cessation attempts.

Overall, a nicotine reduction policy for cigarettes has the potential to dramatically shift the tobacco use landscape in the United States. Results from this study suggest that both menthol and non-menthol smokers could benefit from a nicotine reduction policy via decreases in smoking behavior and toxicant exposure and increases in spontaneous quitting; however, the policy benefits may be greater for non-menthol smokers. Implementing a menthol flavor ban concurrently with a nicotine reduction policy for cigarettes may maximize the public health benefits of cigarette nicotine reduction for menthol smokers.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

Dr. Benowitz reported being a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and being a paid expert witness in litigation against tobacco companies.

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