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# Preliminary evidence on cigarette nicotine reduction with concurrent access to an e-cigarette: Manipulating cigarette nicotine content, e-liquid nicotine content, and e-liquid flavor availability

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## Abstract

The reinforcing characteristics of e-cigarettes could moderate the impact of reducing cigarette nicotine content. In this study, people who smoke daily were recruited from North Carolina and Pennsylvania (US) in 2018 and 2019. Within a randomized 2 × 2 × 2 factorial design, participants received investigational cigarettes and an e-cigarette for 12 weeks. Cigarette nicotine content was very low (0.4 mg/g of tobacco; VLNC) or normal (15.8 mg/g; NNC). E-liquids were 0.3% (“low”) or 1.8% (“moderate”) freebase nicotine, and available in tobacco flavors or tobacco, fruit, dessert and mint flavors. Study recruitment concluded before reaching the

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planned sample size (N=480). Fifty participants were randomized and 32 completed the study. We found that randomization to VLNC, relative to NNC cigarettes, reduced self-reported cigarettes per day (CPD; mean difference: −12.96; 95% CI: −21.51, −4.41; p = 0.005); whereas e-liquid nicotine content and flavor availability did not have significant effects. The effect of cigarette nicotine content was larger in the moderate vs. low nicotine e-liquid groups and in the all flavors versus tobacco flavors e-liquid groups; tests of the interaction between e-liquid characteristics and cigarette nicotine content were not significant. Biomarkers of smoke exposure at Week 12 did not differ across conditions, which may reflect variability in adherence to only using VLNC cigarettes. In conclusion this study offers preliminary evidence that the extent to which cigarette nicotine reduction decreases smoking may depend on the reinforcing characteristics of alternative products, including the available nicotine contents and flavors of e-cigarettes.

## INTRODUCTION

In the landscape of nicotine products, combustible cigarettes are the most toxic and addictive.[1] The U.S. Food and Drug Administration (FDA) has the authority to both 1) limit nicotine reinforcement in cigarettes and 2) regulate the reinforcing characteristics of non-combusted alternative nicotine products that might serve as less harmful substitutes.[2,3] Research studies striving to mimic various FDA policy scenarios can help anticipate potential responses among people who currently smoke.

Several randomized controlled trials have investigated the relationship between cigarette nicotine content and smoking behavior. Replicated across these studies, those assigned very low nicotine cigarettes (VLNC, 0.4 mg per g of tobacco or less) for several weeks smoke fewer average number of cigarettes per day (CPD),[4–7] have lower average cigarette dependence scores and biomarkers of smoke exposure,[4–7] and in some cases, higher quit attempt rates,[5,7] relative to those assigned normal nicotine content cigarettes (NNC, 15.8 mg/g). These results suggest a low nicotine product standard could reduce harm among people who smoke, as intended. However, most cigarette nicotine reduction trials have not incorporated the real-world context in which people who smoke have access to other nicotine products alongside VLNC cigarettes. Since many participants experience initial withdrawal symptoms and have difficulty adhering to the instructions to only use VLNC cigarettes during the trial,[8] we and others hypothesize the availability and characteristics of alternative nicotine products could be important factors in how people who smoke ultimately respond to cigarette nicotine reduction.[9,10]

Electronic nicotine delivery systems (i.e., “e-cigarettes”) are devices that heat a nicotine-infused liquid (i.e., “e-liquid”) to produce an aerosol that can be inhaled (i.e., “vaping”). Unlike most other non-combusted nicotine products, many recent e-cigarettes can offer a pharmacokinetic nicotine delivery profile that matches or exceeds that of cigarettes. [11–13] Both longitudinal e-cigarette use data and evidence from experimental tobacco marketplace purchasing suggest relatively higher e-liquid nicotine content (“strength”) may contribute to the extent to which e-cigarettes substitute for cigarettes.[14–16] E-liquid flavor may also contribute to e-cigarette reinforcement.[16, 17] Until recently, there have been a multitude of e-liquid flavors available, ranging from those that mimic the flavor of menthol and non-

menthol cigarettes (“tobacco flavors”), to many flavors not available in cigarettes including fruit, dessert, candy, nuts, spices, coffee/tea, alcohol, and other beverage options. Among adults who smoke, appealing flavors have been reported as a reason for e-cigarette use and non-tobacco flavors are most commonly used.[17–21] Given that e-cigarettes can mimic (or exceed) the reinforcing potential of regular cigarettes, they may be an especially likely substitute in the event the FDA implements a low nicotine standard for cigarettes. Like cigarette nicotine content, e-liquid nicotine content and flavor availability are subject to FDA regulation. The current study provided people who smoke daily with cigarettes and e-cigarettes for twelve weeks and aimed to assess whether e-liquid nicotine content and e-liquid flavor availability manipulations interacted with cigarette nicotine content to affect smoking and smoke exposure.

## METHODS

### Participants

Between October 2018 and October 2019, participants were recruited from Winston-Salem, NC, Philadelphia, PA and the respective surrounding areas. Eligible participants were at least 18 years old, self-reported smoking between 5 and 50 cigarettes per day for the past month, and provided an expired breath carbon monoxide (CO) reading greater than 10 parts per million (ppm) or a urinary cotinine test indicating greater than or equal to 2000 ng/ml. To avoid enrolling people who likely owned and preferred non-study e-cigarettes, self-reporting frequent use of e-cigarettes (> 15 days in the past month) was exclusionary. However, eligible participants had to report vaping on at least two separate occasions, without an allergic or otherwise adverse experience. Additional eligibility criteria can be found in the Study Protocol (see Supplementary Material). All participants provided written informed consent.

### Study Cigarettes and Vaping Products

Participants received Spectrum research cigarettes[22] matched to their usual brand cigarette menthol preference. Those randomized to the NNC condition received cigarettes with approximately 15.8 milligram nicotine per gram of tobacco. Those randomized to the VLNC condition received cigarettes with approximately 0.4 milligram nicotine per gram of tobacco. Cigarette nicotine content was masked to participants and researchers.

The study e-cigarette provided was a Halo Triton (3.7 V battery; 650 mAh) vape pen and compatible Triton 2.4 ml refillable tanks with 2.2–2.4 ohm coils. E-liquid, sourced from Syndicate Distribution (Westchase, Florida, US) in 10 ml bottles, had a base of 70% propylene glycol and 30% vegetable glycerin. Participants randomized to the “moderate” nicotine content condition received e-liquids with 1.8% freebase nicotine and those randomized to the “low” nicotine content condition received e-liquids with 0.3% freebase nicotine. The corresponding plasma nicotine concentrations achieved among people naïve to vaping, using similar products, suggest these two nicotine levels are distinct.[23,24] The “tobacco flavors” condition included three options reflecting the available flavors of combusted cigarettes (“robust tobacco”, “mild tobacco”, and “menthol/tobacco blend”). The expanded “all flavors” condition included the “tobacco flavors” plus an additional

nine non-tobacco flavors, including fruit (“mixed berry”, “watermelon”, “blueberry”), dessert (“cookies and crème”, “chocolate”, “caramel”) and mint (“peppermint”, “spearmint”, “menthol”) flavors. Both e-liquid nicotine content and flavor were open-label.

## Measures and Procedures

Following screening procedures, eligible participants received an open-label, no cost supply of their usual brand cigarettes to use for a week. They were also enrolled in an automated interactive voice-response (IVR) system, which called participants daily to collect the total number of cigarettes they smoked on the previous day (CPD), distinguishing between cigarettes provided by the study and cigarettes not provided by the study. After a week of establishing baseline smoking rate with their usual cigarettes, participants were randomized within the 2 × 2 × 2 factorial design and began receiving Spectrum study cigarettes and study e-cigarettes. At the randomization visit, participants learned how to use the study e-cigarette and selected up to three e-liquid flavors to use until the next visit. Participants continued receiving study products and reporting daily cigarette use (study and non-study) and daily e-cigarette puffs via the IVR calls for 12 weeks, visiting the lab weekly (Weeks 1–4), and then every other week (Weeks 6, 8, 10, 12). Throughout the study, participants were instructed, encouraged, and incentivized to use only their assigned study cigarettes and e-cigarettes (i.e. no other nicotine products). Empty and partially used study cigarette packs and e-liquid bottles were collected to verify and encourage accurate reporting on IVR calls. At all visits, study staff captured the participant’s vital signs, weight, any changes in health, and an expired breath CO reading to assess cigarette smoke exposure. On the morning of the Week 12 visit, participants collected a first void urine sample. At the Week 12 visit, all participants provided a spot urine sample, returned all study products, and received smoking cessation resources. The first void urine sample was assessed for N-acetyl-S-(2-cyanoethyl) cysteine (CEMA), the mercapturic acid metabolite of acrylonitrile, which serves as a biomarker of cigarette smoke exposure. Anatabine levels from the spot urine samples were quantified and checked against published cut-offs to assess whether participants assigned to VLNC cigarettes adhered to only using VLNC cigarettes.[25] Adherence was confirmed if anatabine levels were 0.014 nmol/ml or below, which is a slightly higher cutoff than what would reflect complete adherence (0.010 nmol/ml) to allow for variation in individual metabolism. Adherence was not assessed in NNC cigarette groups, given the inability to detect metabolite differences between NNC cigarette use and usual brand cigarette use. Additional details about study procedures, measures, and compensation are available in the Study Protocol (see Supplementary Material).

Originally, this study intended to recruit 480 participants, stratifying by age (18 to 24 years old, vs. 25+) and menthol smoking status. However, the deadline for FDA pre-market tobacco product authorizations for e-cigarettes was accelerated by two years, set to occur during the study enrollment period. Enrollment also coincided the emergence and increasing popularity of pod mod devices and nicotine salt formulations.[26] For these reasons it became unclear whether the study e-cigarette and e-liquid would be available for the trial’s duration. Further, given the accrual rate in both this study and our simultaneous 12-week VLNC cigarette marketplace trial, it seemed optimal to consolidate effort to focus on completing

the other study, which has a more adaptive design better suited to continue amid marketplace changes. Thus, we decided to terminate the current study after randomizing 50 participants.

All procedures were approved by the respective Institutional Review Boards at Wake Forest School of Medicine and the University of Pennsylvania and registered on www.clinicaltrials.gov (NCT03185546). Participants could be compensated up to $1070 for completing all study procedures.

### Statistical Analysis

Participants' baseline demographics and smoking characteristics were summarized using mean, standard deviation (SD), frequency and percentage, as appropriate. The primary outcome was average total CPD at Week 12 (which includes both study cigarettes and non-study cigarettes reported via IVR calls). Other outcomes (all measured at Week 12) include average CO, CEMA, having at least one smoke free day, vaping less than 33% of days (aligned with eligibility criteria use) vs. 34–99% days vs. 100% of days, and anatabine levels indicative of adherence for those assigned to VLNC cigarettes. Linear regression models compared CPD, CO and CEMA by condition. For our primary analysis, we fit a linear model that included the main effects for cigarette nicotine content, e-cigarette nicotine content, and e-liquid flavor availability, a baseline measure of the outcome, and the three stratification factors (site, age, and menthol). In addition, we fit separately a model that included the interaction between cigarette nicotine content and e-liquid nicotine content, and another model that included the interaction between cigarette nicotine content and e-liquid flavors. This allowed us to estimate the effect of cigarette nicotine content within levels of the other two factors. More complex models, including multiple two-way interaction and the three-way interaction between factors, were not fit due to the limited sample size. CEMA values were adjusted for creatinine and log-transformed before analysis. With respect to categorical outcomes, Fisher's exact tests were used to compare distribution of participants across conditions. Participants were included in the treatment group to which they were randomized for all analyses, regardless of adherence, and used observed data only, unless otherwise specified. All reported p-values are two-sided and a significance level of 0.05 was used. Analyses were performed in R (version 3.6.1, R Core Team).

## RESULTS

### Demographics

Of the 156 participants consented, 50 were randomized and 32 completed the trial (58% male; mean age 41.6 [SD: 11.7]). Figure S1 details the flow of participation and attrition. The likelihood of study completion did not differ across the 8 experimental groups (p = 0.607). Table S1 shows characterizing information for randomized participants.

### Total CPD

Cigarette nicotine content had significant effects on total CPD at Week 12 (Table 1). Specifically, randomization to VLNC cigarettes, relative to NNC cigarettes, reduced self-reported smoking (mean difference in CPD: −12.96; 95% CI: −21.51, −4.41; p = 0.005). Further, among participants assigned moderate nicotine content e-liquid, those also receiving

VLNC cigarettes reported smoking an average of 22.60 fewer cigarettes than those receiving NNC cigarettes (95% CI: −35.56, −9.64; p = 0.001); whereas in participants assigned low nicotine content e-liquid, those also receiving VLNC cigarettes reported smoking an average of 7.22 fewer cigarettes than those receiving NNC cigarettes (−17.32, 2.87; p = 0.152). However, the interaction term for cigarette nicotine content and e-liquid nicotine content was not statistically significant (p = 0.061). Among participants with access to all e-liquid flavors, those also assigned to VLNC cigarettes smoked an average of 20.81 fewer cigarettes than those assigned NNC cigarettes (−32.37, −9.25; p = 0.001); whereas in participants with access to tobacco e-liquid flavors, those also assigned VLNC cigarettes smoked an average of 7.13 fewer cigarettes than those assigned NNC cigarettes (−17.29, 3.02; p = 0.160). The interaction between cigarette nicotine content and e-liquid flavor was also not statistically significant (p = 0.061).

### Biomarkers of Smoke Exposure

For both CO and CEMA at Week 12, there were no significant main effects for cigarette nicotine content, e-liquid nicotine content and e-liquid flavor (Tables S2 and S3). Participants assigned to moderate nicotine content e-liquid and VLNC cigarettes had lower CO readings (mean difference: −11.78 ppm; 95% CI: −23.98, 0.41; p = 0.058) and lower CEMA levels (−1.26 pmol/mg; −2.49, −0.02; p = 0.047) than those assigned to moderate nicotine content e-liquid and NNC cigarettes. The interactions between cigarette nicotine content and e-liquid nicotine content were not statistically significant (CO p = 0.058; CEMA p = 0.160). The effect of cigarette nicotine content on CO and creatinine-corrected CEMA was similar regardless of flavor condition (Tables S2 and S3). Analyses of CEMA values unadjusted for creatinine showed similar results.

### VLNC Cigarette Adherence

Among study completers, e-liquid nicotine content and flavor availability conditions may have affected adherence to VLNC cigarettes (i.e., not using usual brand cigarettes while participating; Table S4). Assignment to the combination of VLNC cigarettes, moderate nicotine content e-liquid and all flavors resulted in the highest proportion of adherent participants (4/4) and assignment to the combination of low nicotine content e-liquid and tobacco flavors resulted in the lowest proportion of adherent participants (0/4; p = 0.037). When missing values from non-completers were imputed as non-adherent, there were no significant differences between conditions.

### Smoke-Free Days and E-cigarette Use

Among study completers, 7 self-reported at least one smoke-free day during Week 12 (group distribution shown in Table S5). A higher proportion of those receiving moderate nicotine e-liquid reported a smoke-free day (6/15) relative to those receiving low nicotine e-liquid (1/17; p = 0.033). The proportion of participants reporting a smoke-free day did not significantly differ across the full 8 experimental groups (p = 0.188), but among those assigned to the combination of VLNC cigarettes, moderate nicotine e-liquid and all e-liquid flavors had the most participants reporting at least one smoke-free day (3/4), followed by those assigned VLNC cigarettes, moderate nicotine e-liquid and tobacco flavors (2/5).

Nine participants reported using the study e-cigarette less than 33.3% of days (the level of use required for study eligibility), 7 reported use between 33.3 and 99.9% of days, and 16 reported vaping daily (Table S6). The proportion of participants assigned NNC cigarettes vaping daily at Week 12 (5/17) was lower than the proportion of participants assigned VLNC cigarettes (11/15), but this difference was not significant ($p = 0.061$). The overall distribution of participants vaping less than 33.3%, 33.3–99.9% and 100% of days during Week 12 did not significantly differ by experimental condition ($p = 0.086$).

## DISCUSSION

Relative to participants assigned NNC cigarettes, those assigned VLNC cigarettes reported smoking an average of 13 fewer CPD after 12 weeks of use. Due to the early termination of the study, we did not have the statistical power to adequately test interactions between factors. That said, large interactions were observed between cigarette nicotine content and the two e-cigarette characteristic factors, with a larger effect of cigarette nicotine content observed in the moderate nicotine content e-liquid vs. the low nicotine content e-liquid groups and in the all e-liquid flavors groups vs. the tobacco flavors groups. The magnitude of these interactions exceeded that of the hypothesized interactions, for which we powered the original sample size. Nevertheless, interpreting the presence of these interactions remains uncertain due to the small sample size of this trial. Further, the product characteristics of interest (including cigarette nicotine content) did not have significant effects on biomarkers of smoke exposure. Failing to find decreases in markers of smoke exposure, despite reported declines in CPD, may be related to adherence to study cigarette use for groups assigned VLNC cigarettes. Specifically, among participants assigned VLNC cigarettes and low nicotine e-liquid, a minority of participants were adherent and changes in biomarkers were not found; among participants assigned VLNC cigarettes and moderate nicotine e-liquid, a majority of participants were adherent and biomarkers of smoke exposure did decrease. Accordingly, it is possible that non-study cigarette use was under-reported by those in the former group.

The findings of this study should be interpreted within the confines of its limitations. Most notably, the sample was small, and a narrow nicotine use profile was recruited (adults who smoked cigarettes daily and who had tried, but were not regularly using, e-cigarettes), which limits statistical interpretations and generalizability. The e-cigarette chosen for this study differs from the nicotine salt pod mods and disposable e-cigarettes popular today.[26] Future clinical trials investigating cigarette nicotine reduction in the context of alternative products should consider adaptive designs to minimize challenges arising from an ever-changing marketplace.[27] Although not outcomes of interest in this study, expectancies about VLNC cigarettes, relative harm perceptions across products, and differential pricing (taxation) may affect choices between low nicotine cigarettes and alternative nicotine products, and warrant further investigation.[28–30]

In summary, this study provides preliminary evidence that the extent to which a low nicotine product standard in cigarettes reduces smoking may depend on characteristics relevant to the reinforcing potential of alternative nicotine products. Additionally, the extent to which

e-cigarettes displace cigarettes among people who smoke may be aided by reducing the nicotine reinforcement currently available in cigarettes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1.**

Average cigarettes per day (CPD) reported at Week 12.

| | Mean Difference (95% CI) | p-value[1] |
|---|---|---|
| *Main effects model*[1] | | |
| Cigarette Nicotine Content: VLNC (*vs. NNC*) | −12.96 (−21.51, −4.42) | 0.005 |
| E-Liquid Nicotine Content: Moderate (*vs. Low*) | −3.52 (−11.67, 4.64) | 0.383 |
| E-Liquid Flavor Availability: All Flavors (*vs. Tobacco Flavors*) | −2.21, (−10.21, 5.78) | 0.573 |
| *Cigarette Nicotine Content x E-liquid Nicotine Content model*[1] | | 0.061 |
| VLNC vs NNC, Moderate Nicotine E-liquid | −22.6 (−35.56, −9.64) | 0.001 |
| VLNC vs NNC, Low Nicotine E-liquid | −7.22 (−17.32, 2.87) | 0.152 |
| *Cigarette Nicotine Content x E-liquid Flavor Availability model*[1] | | 0.061 |
| VLNC vs NNC, All E-liquid Flavors | −20.81 (−32.37, −9.25) | 0.001 |
| VLNC vs NNC, Tobacco E-liquid Flavors | −7.13 (−17.29, 3.02) | 0.160 |

**Normal Nicotine Content (NNC) Cigarettes**: 15.8 mg nicotine per gram of tobacco

**Very Low Nicotine Content (VLNC) Cigarettes**: 0.4mg nicotine per gram of tobacco

**Moderate Nicotine E-liquid**: 1.8% free-base nicotine

**Low Nicotine E-liquid**: 0.3% free-base nicotine

**All E-liquid Flavors**: 12 flavors available to choose from, including: robust tobacco, light tobacco, tobacco/menthol blend, mixed berry, watermelon, berry, cookies and crème, chocolate, caramel, spearmint, peppermint, and menthol.

**Tobacco E-liquid Flavors**: 3 flavors available to choose from, including: robust tobacco, light tobacco, tobacco/menthol blend.

[1]adjusted for baseline CPD, site, menthol status, and age group