Title

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Journal

Nicotine & Tobacco Research, 24(11)

ISSN

1462-2203

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Publication Date

2022-10-26

DOI

10.1093/ntr/ntac118

Peer reviewed

Nicotine and Tobacco Research, 2022, **24**, 1798–1802
https://doi.org/10.1093/ntr/ntac118
Advance access publication 7 May 2022
Original Investigation

Early Changes in Puffing Intensity When Exclusively Using Open-Label Very Low Nicotine Content Cigarettes

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Abstract

Introduction: In response to reducing cigarette nicotine content, people who smoke could attempt to compensate by using more cigarettes or by puffing on individual cigarettes with greater intensity. Such behaviors may be especially likely under conditions where normal nicotine content (NNC) cigarettes are not readily accessible. The current within-subject, residential study investigated whether puffing intensity increased with very low nicotine content (VLNC) cigarette use, relative to NNC cigarette use, when no other nicotine products were available.

Aims and Methods: Sixteen adults who smoke daily completed two four-night hotel stays in Charleston, South Carolina (United States) in 2018 during which only NNC or only VLNC cigarettes were accessible. We collected the filters from all smoked cigarettes and measured the deposited solanesol to estimate mouth-level nicotine delivery per cigarette. These estimates were averaged within and across participants, per each 24-h period. We then compared the ratio of participant-smoked VLNC and NNC cigarette mouth-level nicotine with the ratio yielded by cigarette smoking machines (when puffing intensity is constant).

Results: Average mouth-level nicotine estimates from cigarettes smoked during the hotel stays indicate participants puffed VLNC cigarettes with greater intensity than NNC cigarettes in each respective 24-h period. However, this effect diminished over time ($p < .001$). Specifically, VLNC puffing intensity was 40.0% (95% CI: 29.9, 53.0) greater than NNC puffing intensity in the first period, and 16.1% (95% CI: 6.9, 26.0) greater in the fourth period.

Conclusion: Average puffing intensity per cigarette was elevated with exclusive VLNC cigarette use, but the extent of this effect declined across four days.

Implications: In an environment where no other sources of nicotine are available, people who smoke daily may initially attempt to compensate for cigarette nicotine reduction by puffing on individual cigarettes with greater intensity. Ultimately, the compensatory behavior changes required to achieve usual nicotine intake from VLNC cigarettes are drastic and unrealistic. Accordingly, people are unlikely to sustain attempts to compensate for very low cigarette nicotine content.

Introduction

Cigarettes deliver nicotine in a rapid, reliable manner that makes them highly addictive.[1] To reduce current cigarette smoking and prevent future uptake, the United States Food and Drug Administration is considering a product standard that would minimize cigarette reinforcement by limiting cigarette nicotine content to very low levels.[2] A potential concern, however, is that people may respond to cigarette nicotine reduction by changing their behavior in ways that increase smoke exposure in an attempt to achieve greater nicotine intake. Possible compensatory behavior changes include both smoking more cigarettes per day and puffing on individual cigarettes with greater intensity (ie, taking more puffs or larger volume puffs).[3,4] Attempting compensation could offset the benefits of a cigarette nicotine reduction policy, at least among people who currently smoke.

Multiple large randomized clinical trials (RCTs) have found that assignment to research cigarettes with very low nicotine content (VLNC; 0.4 mg nicotine per g of tobacco) decreases cigarettes smoked per day without increasing puffing intensity metrics, relative to assignment to research cigarettes with normal nicotine content (NNC; 15.8 mg/g) or usual brand

Received: November 16, 2021. Revised: April 27, 2022. Accepted: May 2 2022.

cigarettes.[5–8] These data mitigate concerns that people will try to circumvent lower nicotine availability through compensatory behavior change. However, although participants in these RCTs were instructed and incentivized to only use the assigned research cigarettes, they ultimately had easy access to regular cigarettes in their usual environment during these studies. As measured by a urinary total nicotine equivalent cutoff in two prominent clinical trials, 76% and 61% of participants assigned to VLNC cigarettes were non-adherent to exclusively smoking VLNC cigarettes.[6,9] Maintaining greater nicotine intake via usual brand cigarette use may prevent attempts to compensate that would occur with exclusive VLNC cigarette use, meaning existing RCTs potentially underestimate compensatory smoking relative to a real-world nicotine reduction scenario where cigarettes with higher nicotine content would presumably be harder to access (ie, via the illicit market).

To learn about responses to exclusive VLNC cigarette use in an environment where NNC cigarettes were not readily accessible, we conducted a study in which participants completed two, separate residential stays at a hotel.[10] During each stay, the only available source of nicotine was research cigarettes; specifically, NNC cigarettes during the first stay and VLNC cigarettes during the second stay. As reported in the primary article, cigarettes smoked per day did not significantly change during the VLNC stay compared to the NNC stay, suggesting that participants did not try to compensate by smoking more cigarettes.[10] The effects of VLNC use relative to NNC use had mixed effects on cumulative biomarkers of smoke exposure. Average expired carbon monoxide and some urinary biomarkers of smoke exposure, such as acrolein metabolite *N*-acetyl-S-(3-hydroxypropyl)-L-cysteine, did not differ across stays. Exposure to acrylonitrile metabolite *N*-acetyl-*S*-(cyanoethyl)-L-cysteine, another urinary biomarker, however was significantly elevated in the first 24-h of the VLNC stay relative to first 24-h of the NNC stay.[10] The objective of the present study was to investigate whether participants puffed VLNC cigarettes with greater intensity.

We used a method whereby we analyzed mainstream smoke solanesol trapped in the cellulose acetate cigarette filter from discarded cigarette filter butts. Solanesol is a long-chain terpenoid naturally occurring in tobacco smoke that is deposited in the filter as a cigarette is smoked.[11] In contrast to many other biomarkers that capture cumulative exposure, the level of solanesol in the discarded filter is a marker of smoke exposure from an *individual cigarette smoked naturally,* and can be used to estimate the level of other smoke constituents delivered directly to users, including nicotine.[11] In our study, the filters from all smoked research cigarettes were collected for analysis. We converted the deposited solanesol level from each individual filter to an estimate of nicotine delivery from that cigarette. To assess whether average puffing intensity was higher when using VLNC cigarettes, we compared the difference in mouth-level nicotine estimates from VLNC and NNC cigarettes smoked by participants smoked to the difference in nicotine delivery that would be expected between VLNC and NNC cigarettes under consistent puffing parameters, segmented by 24-h stay period.

Methods

Participants

Participants were recruited from the Charleston, South Carolina area (United States) in 2018. Major inclusion criteria were (a) ≥18 years old, (b) self-reported smoking 5–30 cigarettes daily for the past month, (c) expired breathe carbon monoxide > 8 parts per million; or a urine cotinine concentration ≥2000 ng/mL, (d) willingness to stay in a local hotel in the later part of 2018. Of the 17 participants who initiated the first hotel stay, 16 completed both stays and were retained for analysis (1 withdrawn due to chest pain during the NNC stay). Full eligibility criteria and a CONSORT diagram of participant flow are reported in the primary article.[10] Participants included in the current analyses were between the ages of 26–63 (mean: 38.87), 50% male, 50% female, 88% White, 6% Black or African–American, 6% other races, and 12.5% Hispanic/Latino/a/x ethnicity. Average baseline cigarettes per day was 14.75 and 44% of participants smoked menthol cigarettes. The study was approved by the Institutional Review Board at the Medical University of South Carolina and registered on www.clinicaltrials.gov (NCT03311646). All participants provided written informed consent.

Hotel Stays

Each participant completed two, four-night hotel stays. For feasibility, participants were scheduled into one of two cohort groups; meaning all participants were in the hotel simultaneously on the same dates as the others in their cohort. Before each stay, everyone reported to the research clinic where study staff confirmed that no nicotine/tobacco products or other substances were packed in their personal belongings. Participants were then transported to the local hotel site. Each stay began at approximately 2:30 p.m. on a Monday and ended at approximately 12:30 p.m. on the subsequent Friday. Participants' daily schedule involved multiple check-ins with study staff at 8:00 a.m., 12:00 p.m., 4:00 p.m., and 8:00 p.m.. All participants stayed in individual, hotel rooms where smoking indoors was explicitly allowed. During each stay all meals were provided, participants could use hotel amenities (eg, hotel pool), and optional activities were available to mitigate boredom (eg, puzzles, coloring books, games). Participants were asked to not fraternize with non-study hotel guests and were required to remain on hotel grounds at all times and to remain in their rooms overnight. Study staff was present at the hotel at all times to help ensure these rules were followed. The two hotel stays were separated by a week-long washout period, during which participants were instructed to smoke as they normally would.

Research Cigarette Access

Throughout each stay, participants only had access to their choice of menthol or non-menthol Spectrum research cigarettes, produced for National Institute on Drug Abuse. The available research cigarettes contained 15.8 mg nicotine/g tobacco (NNC; non-menthol weight of tobacco per cigarette: 0.71 g, menthol weight of tobacco per cigarette: 0.72 g) during the first stay, and 0.4 mg nicotine/g tobacco (VLNC; non-menthol weight of tobacco per cigarette: 0.68 g, menthol weight of tobacco per cigarette: 0.68 g) during the second stay.[5] To maximize external validity, cigarette nicotine content was open-label and participants "purchased" their research cigarette packs from a study store at check-ins with staff. When arriving to the hotel for each stay, participants heard a description of the cigarette nicotine content and received an identical $72.00 account balance to use toward cigarettes during that stay. The price per pack was the same during both stays and approximated the national average at

the time ($6.00 for each NNC and VLNC pack). Thus, the account balance budgeted for purchasing up to three packs per 24-h period. At the end of each stay, participants could return unused cigarettes for reimbursement.

Reimbursements (offered per individual cigarette) and any unused account balance were added to a participant's overall study compensation (an average of $49.00 was reimbursed from unused cigarettes per hotel stay). Average total compensation was $934. Additional information about the descriptions of cigarette nicotine content used and the cigarette purchasing process is detailed in the primary article.[10]

Cigarette Filter Collection

During both hotel stays, participants were instructed to retain the filters from each cigarette smoked. They were provided labeled, re-sealable bags to facilitate collection. At the daily midday check-in with study staff on days 2, 3, 4, and 5, participants turned in all of the filters from cigarettes used in the past 24-h (ie, four 24-h periods). The first cigarette smoked during each hotel stay (Monday afternoon), and the first cigarette smoked each subsequent morning (Tuesday through Friday) were individually stored to allow for additional analyses. A total of 2441 cigarette filters were collected across the two stays. Only two cigarette filters were missed from collection.

Solanesol Analysis and Estimation of Mouth-Level Nicotine Intake

Filter Solanesol Level as a Marker of Mainstream Smoke Exposure

The amount of smoke drawn through a cigarette's filter depends, in part, on puffing intensity metrics, such as puff count, duration, and volume.[7,11,12] As smoke is pulled through the cigarette's filter, chemical constituents including solanesol get deposited there. Given its physical properties, including low volatility and high molecular weight, solanesol is an especially reliable indicator of mainstream smoke exposure. Prior experiments using smoking machines to systematically vary smoke exposure verified that the amount of solanesol trapped by the cigarette filter butt strongly correlates with the amount of mainstream smoke that passed through. For example, filter-level solanesol has a strong positive, linear relationship with machine-generated puff count ($R^2 = 0.985$).[11]

To measure the amount of solanesol in a cigarette filter, a 1-cm portion is cut from the mouth end (below the ventilation holes), and the tipping paper and overwrapping paper is removed. The bare filter segment is spiked with internal standard and solanesol content from the filter is solvent-extracted using agitation of an orbital shaker. Liquid chromatography and quadrupole mass spectrometry are used to quantify solanesol concentration within the extract. This process was conducted for each cigarette collected from participants in this study.[12]

Correlating Filter Solanesol Levels to Estimate Mouth-Level Nicotine Delivery

Like many cigarette constituents, the solanesol content within tobacco varies across cigarette brands. Thus, when smoked by machines under identical puffing intensity parameters, filter level solanesol varies by cigarette brand, which includes differences between menthol and nonmenthol VLNC and NNC Spectrum cigarettes. To accurately determine whether changes in puffing intensity occurred, these brand-level differences need to be accounted for when comparing filter solanesol between the VLNC and NNC cigarettes smoked by participants. One way to do this, is to first convert filter solanesol to a "common currency" of estimated mouth-level nicotine delivery.

Filter solanesol levels can be used to estimate the mouth-level delivery of other nicotine and other smoke constituents.[7,13,14] To generate a solanesol-nicotine correlation curve, filtered cigarettes are smoked by a machine using a variety of different puffing intensity regimens. When machine-smoked, the mainstream smoke particulate matter is trapped on a glass-fiber Cambridge Filter Pad (CFP) while vapor phase constituents pass through the CFP into a gastight bag. Solanesol is extracted and quantified from each cigarette filter butt, nicotine is extracted and quantified from the corresponding CFP, and linear regression is used to describe the extent of the correlation. When applied to filters from cigarettes smoked by human participants, estimates of mouth-level nicotine and tobacco-specific nitrosamines generated by filter solanesol level have been further validated by strong correlations with corresponding urinary biomarkers.[14] Solanesol-nicotine correlation curves are brand-specific have been previously characterized for each type of cigarette used in this study.[7] Accordingly, the amount of solanesol quantified from each cigarette filter collected in the present study was converted to an estimate of mouth-level nicotine using the previously developed, brand-specific, regression equations.

Statistical Analysis

Data analysis focused on whether participants puffed on VLNC cigarettes with greater intensity than NNC cigarettes (i.e. attempting compensation), as indicated by the ratio of mouth-level nicotine estimates from VLNC and NNC cigarettes smoked. The procedures used to generate brand-specific solanesol-nicotine correlation curves described above provide the difference in mouth-level nicotine delivery from a VLNC vs. an NNC cigarette when both are machine-smoked using an identical puffing regimen.[7] This machine-yield ratio is proportional to the different nicotine content of the tobacco used in VLNC and NNC cigarettes and served as a comparison to the average ratio of estimated mouth-level nicotine from VLNC vs. NNC cigarettes smoked by participants. If average smoking intensity is constant across the two cigarette types, we would expect the ratio of average mouth-level nicotine between the two stays to be equal to the machine-yield mouth-level nicotine ratio of VLNC and NNC cigarettes.

For each participant, mouth-level nicotine (mg per cigarette; as estimated from filter solanesol) was summarized by mean and standard deviation for each 24-h period of both hotel stays. To calculate individual-level ratios between stays, we then divided the average value of mouth-level nicotine during each period of the VLNC by the average value mouth-level nicotine in the corresponding period of NNC stay (ie, mean nicotine estimate per cigarette smoked during the first 24-h of the VLNC stay/mean nicotine per cigarette smoked during the first 24-h of the NNC stay, etc.). The natural log of these daily ratios was analyzed using a linear mixed model with separate intercepts for each day and a random effect for individual to account for correlation between data collected on the same participant. We created a compensation index for each 24-h period to summarize changes in puffing intensity, as follows:

$$\text{CompIndex} = 1 - \frac{\text{Within participant VLNC : NNC ratio of mouth level nicotine per cigarette smoked}}{\text{Machine yield VLNC : NNC ratio of mouth level nicotine}} = 1 - \frac{1-e^{\beta_{VLNC,i}}}{1-(N_{VLNC}/N_{NNC})}$$

where $\beta_{VLNC,i}$ is the intercept for 24-h period i for the linear mixed model described above, in which case $e^{\beta_{VLNC,i}}$ can be interpreted as the daily average ratio of mouth level nicotine between stays, and N_{VLNC} and N_{NNC} are the machine-yield mouth-level nicotine values for the VLNC and NNC cigarettes, respectively. We then calculated the corresponding percent change in puffing intensity required when using VLNC cigarettes, vs VLNC cigarettes, to achieve the participants' average mouth-level nicotine ratios.

$$\%\ \text{Change in puffing intensity} = \frac{e^{\beta_{VLNC,i}}}{(N_{VLNC}/N_{NNC})} - 1$$

Again, $e^{\beta_{VLNC,i}}$ can be interpreted as the daily average ratio of mouth level nicotine between stays, and N_{VLNC}/N_{NNC} is the ratio of machine-yield nicotine levels for the VLNC and NNC cigarettes. If the average ratio in estimated mouth-level nicotine delivery between cigarettes smoked by participants during VLNC and NNC stays is lower than the ratio determined by machine yield, it means that puffing intensity increased (eg, participants inhaled more deeply, or took more frequent puffs when using VLNC cigarettes vs NNC cigarettes). 95% confidence intervals were calculated and significance was established if the interval did not include zero. In a secondary analysis, 24-h period was treated as a continuous variable in the linear mixed model to evaluate percent change in puffing intensity trends across time. It is important to note that because the nicotine content of VLNC cigarettes is so low, even seemingly small differences in mouth-level nicotine estimates relative to the machine-yield ratio would require substantial increases in puffing intensity. Finally, average change puffing intensity was also analyzed separately for the cigarettes smoked after periods of overnight abstinence (eg, the first cigarette of the hotel stays and the first cigarette smoked each morning).

Results

When exclusively using NNC cigarettes, the average filter solanesol level per cigarette was 70.055 µg (standard deviation: 23.975) in the first 24-h period, 71.051 µg (25.181) in the second 24-h period, 69.930 µg (28.437) in the third 24-h period, and 74.700 µg (28.710) in the final 24-h period. These values correspond to average participant mouth-level nicotine estimates of 0.997 mg (0.320), 1.006 mg (0.337), 0.990 mg (0.384), and 1.048 mg (0.385) per cigarette, respectively (Table S1). When exclusively using VLNC cigarettes, the average filter solanesol level per cigarette was 48.353 µg (16.815) in the first 24-h period, 43.431 µg (14.100) in the second 24-h period, 43.800 µg (16.024) in the third 24-h period and 41.811 µg (17.213) in the final 24-h period. These values correspond to average mouth-level nicotine estimates of 0.0.39 mg (0.013), 0.035 mg (0.010), 0.036 mg (0.012), and 0.034 mg (0.013) per cigarette (Table S1). Figure 1 shows the percent average change in puffing intensity per cigarette needed to achieve the mouth-level nicotine estimates for each 24-h period of the VLNC stay, relative to each 24-h period of the NNC stay, with accompanying 95% confidence intervals. As shown, VLNC cigarette puffing intensity (vs. NNC cigarette puffing intensity) was 40.0% (95% CI:29.9,53.0) greater than in the first 24-h period, 26.3% (16.4, 37.1) greater in the second 24-h period, 29.9% (19.7, 41.0) greater in the third 24-h period, and 16.1% (6.9, 26.0) greater in the fourth period. The trend of this effect lessening across time was statistically significant ($p < .001$). When separately analyzing the average change in puffing intensity among only a subset of cigarettes that included the first cigarette participants smoked at each hotel stay and the first cigarette smoked each subsequent morning, the increase in VLNC puffing intensity, relative to NNC puffing intensity, was greatest on day 3 (+48.7%; 20.7, 83.3) and smallest on day 5 (+15.8%; –6.0, 42.7; Table S2). A sensitivity analysis excluding these cigarettes from the overall comparison of smoking intensity between stays did not meaningfully alter the reported results.

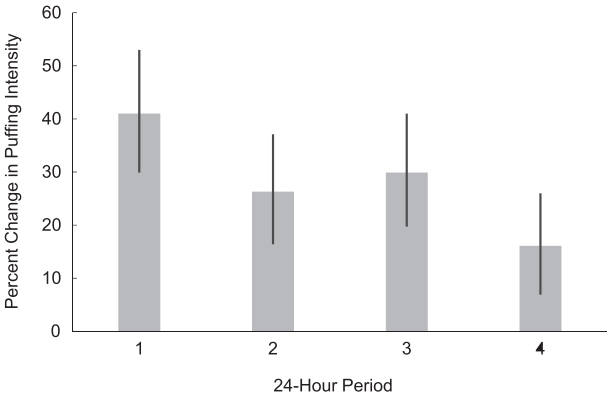

Figure 1. The percent change in puffing intensity per cigarette when using very low nicotine content cigarettes, relative to normal nicotine content cigarettes, required to achieve the ratio of mouth-level nicotine estimated by solanesol quantification in used cigarette filters (with 95% confidence interval). Each 24-h period represents from approximately 12 p.m. on Monday to 12 p.m. on Friday.

Discussion

Mouth-level nicotine estimates, derived from the level of solanesol deposited in used cigarette filters, suggest that switching to exclusive very low nicotine cigarette use may produce initial increases in puffing intensity per cigarette, but this effect diminished over the study period. Furthermore, importantly, total smoke exposure is a product of both puffing intensity and the quantity of cigarettes consumed. The results reported here capture differences in puffing intensity patterns by averaging across individual cigarettes, but do not account for cigarettes per day. As reported in the primary article, average cigarettes per day and expired CO levels (a relatively transient measure of smoke exposure) did not differ between any 24-h period of the VLNC cigarette and NNC cigarette stays.[10] Urinary biomarkers of smoke exposure, which reflect the impact of both cigarettes per day and puffing intensity, showed that some analytes (eg, hydroxypropyl-MA, Mandelic acid, trans-Muconic acid, Phenylglyoxylic acid), but not all (eg, cyanoethyl-MA), were elevated in the first 24-h of the VLNC cigarette stay relative to the first 24-h of the NNC cigarette stay. Additionally, no biomarkers of exposure were significantly elevated during the VLNC stay relative to the NNC stay in the last 24-h period, and some were significantly reduced.[10] Overall, the biomarker data from this study do not indicate a sustained expose to greater levels of smoke when exclusively using

VLNC cigarettes compared with NNC cigarettes over a four-day period.

Participants may initially change their puffing behavior when nicotine content is reduced because smoking VLNC cigarettes offers a different sensory experience than smoking NNC cigarettes. Compensatory changes in puff topography have been observed among participants sampling VLNC cigarettes with masked nicotine content, in a laboratory setting.[8] Participants may also alter puffing intensity because they anticipate needing more nicotine. Being told a cigarette has VLNC, regardless of its actual nicotine content, can change acute puffing behavior.[15] Some participants in the current study reported in qualitative interviews that they thought they would need to smoke more cigarettes or puff more intensely at the beginning of the VLNC stay.[16] However, increases in puffing intensity are likely not sustained over time because achieving a usual amount of nicotine intake from 0.4 mg/g VLNC cigarettes through changes in inhalation is not feasible, even with a drastic multi-fold increases in puffing intensity.[17]

The current study is limited by a relatively small participant pool, and short duration. Additionally, the order of NNC and VLNC conditions was not counterbalanced, but this aligns with a mandated policy scenario in which people who smoke would transition from NNC to VLNC cigarettes. Though every effort was made to ensure participants only used cigarettes provided by the study while staying at the hotel, two participants had urinary total nicotine equivalents and anatabine levels indicative of non-adherence (ie, using regular cigarettes) during the VLNC stay.[10] Sensitivity analyses removing those two participants did not alter the reported effects herein. Ultimately, study designs that effectively mimic the realistic availability of other nicotine sources (ie, vaping products, oral products, and nicotine replacement therapies), are best suited to anticipate the effects of cigarette nicotine reduction policy on smoking intensity and compensation. Nonetheless, our findings suggest initial, but declining, increases in average puffing intensity per cigarette with exclusive VLNC cigarette use.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

Funding

This study was funded by National Institute on Drug Abuse (NIDA) R03DA045197—Smith. Author support also included NIDA R36DA054481—White. The discarded filter analysis work was supported by funding from the Centers for Disease Control and Prevention, an operating division of the U.S. Department of Health and Human Services. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service, or the U.S. Department of Health and Human Services. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Department of Health and Human Services or any of its affiliated institutes or agencies.

Declaration of Interests

Benowitz has been a consultant to Achieve Life Sciences and Pfizer, companies that market or are developing smoking cessation medications, and has been a paid expert witness in litigation against tobacco companies. Carpenter has received consulting honoraria from Pfizer and Frutarom.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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