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Brief Report

Nicotine Delivery and Changes in Withdrawal and Craving During Acute Electronic Cigarette, Heated Tobacco Product, and Cigarette Use Among a Sample of Black and White People Who Smoke

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Abstract

Introduction: E-cigarettes and heated tobacco products (HTPs) may serve as potential options for harm reduction for smokers if they possess reward profiles similar to cigarettes. Little is known about the abuse liability of HTPs and e-cigarettes versus cigarettes in racial/ethnic minority smokers.

Aims and Methods: Twenty-two nicotine-deprived people who smoke (black [n = 12] and white [n = 10]) completed three visits that included a standardized 10-puff bout followed by a 50-minute ad libitum use assessment with their usual brand cigarette (UBC), an e-cigarette, and HTP. Visits were completed in a randomized crossover design and were separated by a minimum 48-hour washout period. Assessments included plasma nicotine, Cmax, and reductions in craving and withdrawal.

Results: UBC delivered significantly greater levels of nicotine compared to the e-cigarette ($p < .001$) and HTP ($p < .01$) during both the standardized and ad libitum sessions. HTP delivered more nicotine than the e-cigarette during the standardized puffing session ($p = .047$) but not the ad libitum session. Only craving during the standardized puffing session and not the ad libitum session showed significant differences across products ($p < .001$) such that UBC resulted in the greatest reduction followed by HTP and e-cigarette.

Conclusions: Despite greater nicotine delivery from the UBC compared to e-cigarette and HTP, participants reported reductions in craving and withdrawal across products, particularly following ad libitum use.

Implications: Use of participant's UBCs (UBC) resulted in greater nicotine delivery compared to both the e-cigarette and HTP. Despite this relative difference in nicotine delivery, participants reported reductions in craving and withdrawal across products, particularly following ad libitum use. These findings suggest that in this sample of black and white people who smoke, HTPs and e-cigarettes provided significant relief from negative symptoms that maintain smoking.

Introduction

People who smoke are motivated to quit and over half attempt to quit each year, yet <10% are successful.[1] For people who smoke and are unable or unwilling to quit, alternative products with potentially reduced harm (eg, e-cigarettes and heated tobacco products [HTP]) may be options to lower tobacco-related toxicant exposure and reduce short- and possible long-term tobacco-related negative health effects.[2–4]

For alternative products to be viable substitutes for combustible cigarettes, they must mimic cigarettes' reinforcement profile.[5,6] Findings from studies examining e-cigarettes and HTPs remain mixed in terms of nicotine delivery and resulting reductions in symptoms of craving and withdrawal, largely because of differences in methods, types or generations of devices, and study populations. Two small-scale studies have been conducted comparing nicotine delivery of pod salt-based e-cigarettes and IQOS HTP to combustible cigarettes among smokers[7,8] and showed that e-cigarettes and IQOS deliver significant nicotine but less so than combustible cigarettes. These studies necessitate replication and extension to include a more complete assessment of the pharmacokinetic profiles of these products among a diverse sample of people who smoke.

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Despite smoking fewer cigarettes per day, black people who smoke bear a disproportionate greater burden of smoking-related disease and death.[9] With the emergence of e-cigarettes and HTPs, studies are needed that explicitly and purposefully examine the pharmacokinetic profile of alternative products among black people who smoke.

Materials and Methods

The pilot study was completed from September 2020 to August 2021. Participants were recruited from the Kansas City, MO area. Eligible participants were at least 21 years old, smoked 5–30 cigarettes per day, smoked at their current rate for at least 6 months, were not motivated to quit smoking, and had limited experience with the alternative products (used < 5 times in their lifetime). See Supplementary Figure S1 for study Consort Diagram.

Study Products

Participants were provided with the study e-cigarette (JUUL in 5% nicotine) and HTP (IQOS) at no cost. Participants were given the choice between menthol or tobacco e-liquid for the e-cigarette and smooth menthol (lighter menthol flavor), fresh menthol (stronger menthol flavor), or tobacco flavor for the HTP. Participants tried the flavors in the lab before choosing.

Procedures

This was a pilot randomized 3-period 2-sequence crossover study in which pharmacokinetic assessments were performed for participants' usual brand cigarette (UBC), a study-provided e-cigarette and HTP. Participants used their UBC at visit (period) one and were randomly assigned to the order in which they used the e-cigarette and HTP at the two subsequent visits. UBC was used at visit one to allow participants to be trained on use of the new study products at the end of the visit and to allow time for home practice prior to the visits during which they would use one of them. Participants were instructed to remain tobacco/nicotine abstinent for 12 hours prior to each study visit. Abstinence was biochemically confirmed via expired carbon monoxide (eCO) ≤12 ppm.[10] Participants completed written informed consent. All study procedures were reviewed and approved by the University of Kansas Medical Center's Institutional Review Board.

At the first visit, participants completed baseline self-report measures including demographics, smoking history, and nicotine dependence.[11] The remainder of the visits were identical except for the product used. At each visit, participants completed a standardized 10-puff bout followed by a 50-minute ad libitum session. The 10-puff bout and ad libitum sessions were separated by a 10-minute rest during which no puffs were taken (Supplementary Figure S2). During the 10-puff bout, they were instructed to take a puff every 30 seconds, resulting in 10 puffs over 5 minutes. Blood draws for serum nicotine concentration, and assessments of craving (QSU-Brief)[12,13] and withdrawal (MNWS),[14,15] occurred at 0 minutes (pre-10-puff bout), 5 minutes (immediately following 10-puff bout), 7 minutes, 15 minutes, and at the end of the ad libitum smoking or vaping session. Plasma nicotine samples were analyzed by UPLC-MSMS method, and validated according to GLP method acceptance criteria.

At the end of the UBC study visit, participants were shown how to use and charge the next device. Participants were asked to document practice 2–3 times per day on a practice form. Participants who did not return the completed form were not allowed to complete the visit. Participants were compensated $50 for visit one, an additional $6 for bringing a pack of their cigarettes, $75 for visit two, $100 for visit three, and up to $50 for completing all study visits and adhering to study procedures.

Data Analytic Plan

To mitigate the impact of multiple comparisons, we calculated the area under the curve (AUC) of plasma nicotine levels versus time for each product, combining the observations at 0, 5, 7, and 15 minutes with the trapezoidal rule ($AUC_{0\text{-}15}$). Analogous AUCs were calculated for withdrawal and craving versus time. To adjust for nicotine levels, both the AUCs for craving and withdrawal were divided by their corresponding nicotine AUC. Thus, a craving or nicotine AUC ratio is interpreted as the amount of craving per unit of delivered nicotine. Maximum nicotine levels (Cmax) achieved during the first 15 minutes were also calculated. Because of the right-skewed nature of the AUC distribution, a log-gamma random-intercept linear regression model of nicotine AUC was fitted to compare the amount of nicotine delivered across products.[16] The model included dummy variables for e-cigarettes and HTP as independent variables, using UBC as the reference variable. Analogous models were fitted to compare craving and withdrawal scores, craving/nicotine and withdrawal or nicotine AUC ratios, and Cmax across products.

To analyze ad libitum outcomes, we fit a random-intercept linear model of nicotine levels immediately following the ad libitum session, adjusting for nicotine $AUC_{0\text{-}15}$. Similar models were fit for craving and withdrawal scores immediately following the ad libitum session, log-transforming the responses to achieve model assumptions. Residual analyses and predicted values were used to examine the goodness-of-the-fit of the models. Statistical tests were conducted at a 0.05 significance level. Data analyses were performed using Stata 17.0 and SPSS v27.

Results

Participant Characteristics and Smoking History

Participants were 22 adults who smoked (black/African American, 12; white, 10). Thirteen participants self-identified as female (59.1%). The mean age was 54.1 years (SD = 12.0; range: 24–65 years). See Table 1 for baseline characteristics.

Nicotine Delivery

Ten-Puff Bout Session

Significant differences emerged in nicotine $AUC_{0\text{–}15}$ by product ($X^2 = 23.37$, $df = 2$, $p < .001$). Specifically, UBC delivered significantly greater nicotine (mean $AUC_{0\text{–}15}$, 147.4 ng/mL; 95% CI, [104.5, 190.3]) compared to both e-cigarettes (66.9 [47.3, 86.4]) and HTPs (91.7 [65.4, 117.9]) during the 10-puff bout (Table 2). Nicotine AUC was 120.5% greater for UBC compared to e-cigarettes ($p < .001$) and 60.8% greater for UBC compared to HTPs ($p = .003$). Moreover, nicotine AUC was 37.1% greater for HTPs compared to e-cigarettes ($p = .047$). Supplementary Figure S3 depicts nicotine delivery by product.

Similarly, significant differences in nicotine $Cmax_{0\text{–}15}$ resulting from the 10-puff bout emerged across products ($X^2 = 22.47$, $df = 2$, $p < .001$; Table 2). UBC yielded significantly greater maximum nicotine levels (mean $Cmax_{0\text{–}15}$, 14.9 ng/mL; 95% CI, [10.1, 19.7]) compared to both

Table 1. Participant Characteristics ($N = 22$)

Characteristic	Mean	SD
Age (y)	54.1	12.0
Average cigarettes per day	15.9	9.2
	n	%
Gender		
Female	13	59.1
Male	9	40.9
Race		
Black/African American	12	54.5
White	10	45.5
Education		
Some high school	4	18.2
Grade 12 or GED	7	31.8
College 1 year to 3 years	8	36.4
College 4 years or more	3	13.6
Annual household income		
<$25 000	14	63.6
$25 000 to <$50 000	5	22.7
$50 000 to <$75 000	1	4.5
$100 000 or more	1	4.5
Refused to answer	1	4.5
Employment status		
Unemployed	7	31.8
Employed full time	3	13.6
Retired	7	31.8
Disabled	5	22.7
Home ownership		
No	20	90.9
Yes	2	9.1
Smoke within 30 min of waking	17	77.3
Menthol smoking		
Menthol	15	68.2
Non-menthol	7	31.8

GED = General Educational Development Test; TTFC = Time to first cigarette.

e-cigarettes (6.4 [4.3, 8.4]) and HTPs (9.0 [6.2, 11.9]) during the 10-puff bout (Table 2). UBC showed 134.4% ($p < .001$) and 65.2% ($p = .004$) greater nicotine $Cmax_{0–15}$ compared to e-cigarettes and HTPs, respectively. Nicotine $Cmax_{0–15}$ was 41.9% greater for HTPs compared to e-cigarettes ($p = .044$).

Ad libitum Session

After adjusting for nicotine $AUC_{0–15}$ (ie, nicotine levels after the 10-puff bout), significant differences in nicotine levels following the ad libitum period emerged ($X^2 = 97.7$, $df = 2$, $p < .001$). Specifically, UBC ad libitum use resulted in significantly greater nicotine levels compared to e-cigarettes (mean difference, 7.3 ng/mL; 95% CI, [4.3, 10.4]; $p < .001$) and HTPs (mean difference, 6.5 ng/mL; 95% CI, [3.7, 9.4]; $p < .001$). However, no significant differences were observed in nicotine levels following ad libitum use between e-cigarettes and HTPs ($p = .54$; Supplementary Figure S3).

Cigarette Craving

Ten-puff Bout Session

Before adjusting for nicotine levels, no significant differences in craving AUC_{0-15} across products were seen ($X^2 = 1.68$, $df = 2$, $p = .43$; Table 2). However, after adjusting for the amount of nicotine delivered, significant differences in cigarette craving $AUC_{0–15}$ emerged across products ($X^2 = 22.42$, $p < .001$; Table 2). Specifically, mean craving/nicotine AUC_{0-15} ratio was 2.8 times higher when using e-cigarettes compared to UBC ($p < .001$), and the ratio under HTPs was 1.7 times higher than under UBC ($p = .013$), suggesting that UBCs were more effective in reducing craving compared to both e-cigarettes and HTP. Moreover, the mean craving/nicotine $AUC_{0–15}$ ratio was 1.6 times higher when using e-cigarettes compared to HTP ($p = .017$), suggesting that HTP was more effective at suppressing craving compared to e-cigarettes. Supplementary Figure S4 depicts cigarette craving by product and Supplementary Figure S5 shows craving/nicotine $AUC_{0–15}$ ratios.

Ad libitum Session

After adjusting for craving $AUC_{0–15}$, there were no significant differences in craving scores across products following the ad libitum session ($p = .67$; Supplementary Figure S4).

Table 2. Means and 95% CIs for the Study Outcomes Encompassing the 10-puff Bout Session (5 Minutes) and Subsequent Resting Session (10 minutes)[a]

Outcome	UBC	e-Cigarettes	HTP	p-value[b]
Nicotine $AUC_{0–15}$ [ng/(mL × min)]	147.4 (104.5, 190.3)	66.9 (47.3, 86.4)	91.7 (65.4, 117.9)	<0.001
Nicotine Cmax, 0–15 min [ng/mL]	14.9 (10.1, 19.7)	6.4 (4.3, 8.4)	9.0 (6.2, 11.9)	<0.001
Craving AUC_{0-15} [min^{-1}]	365.5 (274.1, 456.8)	423.0 (317.1, 528.8)	397.9 (298.3, 497.4)	0.43
Craving/nicotine AUC_{0-15} ratio [mL/ng]	3.3 (1.8, 4.8)	9.1 (5.0, 13.3)	5.6 (3.1, 8.1)	0.001
Withdrawal $AUC_{0–15}$ [min^{-1}]	67.7 (34.5, 100.9)	42.3 (21.1, 63.5)	45.7 (23.1, 68.3)	0.071
Withdrawal/nicotine $AUC_{0–15}$ ratio [mL/ng]	0.67 (0.28, 1.05)	0.95 (0.39, 1.50)	0.72 (0.30, 1.14)	0.45

CI = confidence interval; AUC_{0-15} area under the curve calculated with observations at 0, 5, 7, and 15 minutes; Cmax = maximum observed concentration.
[a]Means were calculated with random-intercept log-gamma regression models, and confidence intervals with the delta method.
[b]*p*-value from a Wald chi-square test with 2 °C of freedom.

Withdrawal Symptoms

Ten-puff Bout Session

Before adjusting for nicotine levels, no significant difference in cigarette withdrawal AUC_{0-15} across products was seen ($X^2 = 5.29$, $df = 2$, $p = .07$). Furthermore, there were no significant differences in the withdrawal/nicotine AUC_{0-15} ratios across products ($X^2 = 1.58$, $df = 2$, $p = .45$; Table 2 and Supplementary Figure S6), indicating that, regardless of adjustment for nicotine delivery, all three products produced comparable reductions in nicotine withdrawal as a result of the 10-puff bout. Supplementary Figure S7 depicts withdrawal symptoms by product.

Ad libitum

After adjusting for withdrawal AUC_{0-15}, there were no significant differences in withdrawal across products following the ad libitum session ($p = .49$; Supplementary Figure S7).

Discussion

The findings from the current study are consistent with previous studies[7,8] and suggest that despite relatively lower nicotine delivery among new users, the alternative products still provide significant relief from negative symptoms that maintain smoking. Moreover, data suggest that established e-cigarette users can achieve cigarette-like levels of nicotine delivery.[17] In controlled studies, e-cigarettes have been shown to facilitate smoking cessation and may outperform some FDA-approved medications.[18] In a recent randomized trial of refillable e-cigarettes versus HTPs for smoking cessation among people who smoke but were uninterested in quitting, both products resulted in significant reductions in cigarette consumption at 12-week follow-up.[19]

The combusted tobacco endgame approach envisions a world in which cigarettes are abolished.[20] Acceptable substitutes for adults who smoke are likely to be an important component in achieving this endgame. The current research suggests that both e-cigarettes and HTP could serve this important function. There may be benefit to having many potentially reduced harm products available to give adults who smoke the best chance possible at harm reduction.

Limitations of the study included a relatively small sample of black and white people who smoke, the assessment was limited to a single e-cigarette and HTP, and the HTP used in the current study is not currently available for sale in the U.S. market.

Despite relatively lower nicotine delivery, the e-cigarette and HTP significantly reduced symptoms of craving and withdrawal following ad libitum use and did so to a similar extent as cigarettes. In conjunction with existing studies, this research suggests that when people who smoke are allowed to use the product as they would in a real-world environment (ie, ad libitum), e-cigarettes and HTPs may be viable substitutes for cigarettes for black and white people who smoke. Research is needed to understand how data on acute use among people who currently smoke will translate to longer-term switch outcomes.

Supplementary Material

Supplementary material is available at Nicotine and Tobacco Research online.

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Declaration of Interests

None to disclose.

Author Contributions

Eleanor Leavens (Conceptualization [Lead], Data curation [Equal], Funding acquisition [Lead], Investigation [Equal], Methodology [Equal], Project administration [Equal], Visualization [Supporting], Writing—original draft [Lead], Writing—review & editing [Equal]), Leah Lambart (Investigation [Equal], Methodology [Equal], Project administration [Equal], Writing—review & editing [Equal]), Francisco Diaz (Data curation [Equal], Formal analysis [Lead], Visualization [Lead], Writing—original draft [Supporting], Writing—review & editing [Equal]), Theodore Wagener (Conceptualization [Equal], Investigation [Equal], Methodology [Equal], Writing—review & editing [Equal]), Jasjit Ahluwalia (Conceptualization [Equal], Investigation [Equal], Methodology [Equal], Writing—review & editing [Equal]), Neal Benowitz (Conceptualization [Equal], Investigation [Equal], Methodology [Equal], Writing—review & editing [Equal]), and Nikki Nollen (Conceptualization [Equal], Funding acquisition [Equal], Investigation [Equal], Methodology [Equal], Resources [Equal], Supervision [Lead], Visualization [Supporting], Writing—review & editing [Equal]).

Data Availability

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

References

1. Creamer MR, Wang TW, Babb S, *et al*. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(45):1013.
2. Sakaguchi C, Nagata Y, Kikuchi A, Takeshige Y, Minami N. Differences in levels of biomarkers of potential harm among users of a heat-not-burn tobacco product, cigarette smokers, and never-smokers in Japan: A post-marketing observational study. *Nicotine Tob Res*. 2021;23(7):1143–1152.
3. Gale N, McEwan M, Camacho OM, Hardie G, Proctor CJ, Murphy J. Changes in biomarkers after 180 days of tobacco heating product use: A randomised trial. *Intern Emerg Med*. 2021;16(8):2201–2212.
4. National Academies of Science, Engineering, and Medicine. *Public health consequences of e-cigarettes*. Washington, DC, USA: National Academies Press; 2018.

5. Leavens EL, Nollen NL, Ahluwalia JS, *et al*. Changes in dependence, withdrawal, and craving among adult smokers who switch to nicotine salt pod-based e-cigarettes. *Addiction*. 2022;117(1):207–215.
6. Abrams DB, Glasser AM, Villanti AC, *et al*. Managing nicotine without smoke to save lives now: Evidence for harm minimization. *Prev Med*. 2018;117:88–97.
7. Phillips-Waller A, Przulj D, Pesola F, Smith KM, Hajek P. Nicotine delivery and user ratings of IQOS heated tobacco system compared with cigarettes, Juul, and refillable e-cigarettes. *Nicotine Tob Res*. 2021;23(11):1889–1894.
8. Maloney S, Eversole A, Crabtree M, *et al*. Acute effects of JUUL and IQOS in cigarette smokers. *Tob Control*. 2021;30(4):449–452.
9. Haiman CA, Stram DO, Wilkens LR, *et al*. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med*. 2006;354(4):333–342.
10. Sandberg A, Skold CM, Grunewald J, Eklund A, Wheelock AM. Assessing recent smoking status by measuring exhaled carbon monoxide levels. *PLoS One*. 2011;6(12):e28864.
11. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The fagerström test for nicotine dependence: A revision of the fagerstrom tolerance questionnaire. *Br J Addict*. 1991;86(9):1119–1127.
12. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res*. 2001;3(1):7–16.
13. Toll BA, Katulak NA, McKee SA. Investigating the factor structure of the Questionnaire on Smoking Urges-Brief (QSU-Brief). *Addict Behav*. Jul 2006;31(7):1231–1239.
14. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry*. Mar 1986;43(3):289–294.
15. Toll BA, O'Malley SS, McKee SA, Salovey P, Krishnan-Sarin S. Confirmatory factor analysis of the Minnesota Nicotine Withdrawal Scale. *Psychol Addict Behav*. 2007;21(2):216–225.
16. Arrojo-Romero M, Barbazán CA, López-Moriñigo JD, *et al*. Caffeine consumption in a long-term psychiatric hospital: Tobacco smoking may explain in large part the apparent association between schizophrenia and caffeine use. *Schizophr Res*. 2015;164(1-3):234–241.
17. Wagener TL, Floyd EL, Stepanov I, *et al*. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control*. 2017;26(e1):e23–e28.
18. Hartmann-Boyce J, McRobbie H, Butler AR, *et al*. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2021(9):1–248.
19. Caponnetto P, Campagna D, Maglia M, *et al*. Comparing the effectiveness, tolerability, and acceptability of heated tobacco products and refillable electronic cigarettes for cigarette substitution (CEASEFIRE): Randomized controlled trial. *JMIR Public Health Surveill*. 2023;9(1):e42628.
20. Smith EA, Malone RE. An argument for phasing out sales of cigarettes. *Tob Control*. 2020;29(6):703–708.