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Use Behaviors, Dependence, and Nicotine Exposure Associated with *Ad Libitum* Cigar Smoking

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Abstract

Objectives—To examine factors important to cigar smoking and subsequent nicotine exposure, we evaluated the impact of cigar type, cigarette smoking history, and inhalation behaviors on nicotine dependence, smoking topography, and biomarkers of exposure in current exclusive cigar smokers.

Methods—Adult, exclusive cigar smokers (N = 77) were recruited based on cigar type, cigarette smoking history, and self-reported inhalation behaviors. Participants smoked their own brand product *ad libitum* for up to one hour; dependence symptoms, smoking topography, and biomarkers of exposure were assessed.

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Human Subjects Approval Statement

The Quorum Review IRB and the Food and Drug Administration's Research Involving Human Subjects Committee approved this study.

Conflict of Interest Disclosure Statement

All authors of this article declare they have no conflicts of interest.

Disclaimer

This publication represents the views of the author(s) and does not represent FDA/CTP position or policy.

Results—Cigar smokers showed low levels of dependence. Cigar smoking alleviated withdrawal and craving symptoms, increased plasma nicotine concentration, and increased exhaled CO. Multiple regression analyses indicate that inhalation behaviors were associated with increased dependence and greater reductions in withdrawal symptoms upon cigar smoking. Large cigar smokers smoked longer and smoked more tobacco than small cigar and cigarillo smokers. Furthermore, large cigar smokers and self-reported inhalers were exposed to more nicotine than small cigar smokers and non-inhalers.

Conclusions—Our study suggests that cigar type and smoking behaviors affect dependence and nicotine exposure upon cigar smoking. These findings provide additional insight into the substantial risks associated with cigar smoking.

Keywords

cigars; smoking; tobacco; addiction; biomarkers

Cigar smoking constitutes a significant public health concern. Whereas cigarette smoking has decreased significantly over the past 2 decades, cigar consumption has remained relatively stagnant.¹ To protect public health, the Food and Drug Administration's (FDA) Center for Tobacco Products (CTP) now has regulatory authority over all cigars under the Family Smoking Prevention and Tobacco Control Act. In part, this rule prohibits the sale of cigars to people younger than age 18 and requires nicotine/addiction warning statements on cigar labels or at the point of sale.

Although lacking formal classifications, cigars are commonly grouped into 3 categories based on product characteristics such as weight, size, and use of filter tips.² Small cigars tend to look and feel like cigarettes; cigarillos are long and slim, weighing approximately 3g; large cigars are notably distinct from cigarettes and are the heaviest cigars.

Increases in cigar consumption may be due in part to the lower overall cost of some cigars compared to cigarettes (resulting from lower excise taxes on cigars) as well as a perception that cigars are less harmful or addictive than cigarettes.^{3,4} However, these perceptions are at odds with the limited scientific literature that has investigated nicotine content and the abuse potential of these tobacco products. Indeed, cigars may contain between 6 and 335 mg of nicotine, the primary addictive chemical in tobacco, depending on cigar size and amount of tobacco⁵—often well above the average nicotine content in cigarettes, 7–18 mg. As flexible nicotine delivery tobacco products, cigars also may deliver similar or greater amounts of nicotine compared to other tobacco products that cause dependence.⁶ Therefore, cigar smokers may show dependence symptoms that are similar to those of cigarette smokers and other tobacco product users.⁷

However, the impact of cigar smoking on dependence symptoms and use behaviors has been explored only recently. Some studies have examined the abuse potential of cigars by assessing craving and withdrawal symptoms, and have demonstrated that cigar smoking effectively alleviates many of these symptoms.^{8–12}

Another important factor in determining abuse potential is nicotine exposure, which may be influenced individually through specific use behaviors. The topography of cigar smoking has been evaluated in dual cigar and cigarette smokers; use behaviors differ across cigar products, suggesting that smokers may adapt their topography based on cigar characteristics. Several studies also have examined biomarkers of exposure in cigar smokers, and have noted that cigar smoking is associated with significant nicotine exposure.^{8–14}

Due to differences in nicotine content, it is likely that cigar type influences dependence and nicotine exposure, although no studies have examined these differences among cigar types. Two other factors are also likely important. First, former cigarette smoking may influence smoking behavior and inhalation;¹⁵ cigarette smoking history also may impact nicotine exposure and physiological measurements.^{10,16} Furthermore, although cigar smoke is more alkaline and, therefore, more aversive than cigarette smoke,^{5,16,17} several studies have found at least mild inhalation in small cigar, cigarillo, and large cigar smokers by measuring serum thiocyanate or exhaled carbon monoxide (CO).^{18–20} Additional research indicates that cigar smoke inhalation significantly influences nicotine absorption rate and plasma concentrations.^{19,21}

Studying cigar use is difficult due, in part, to product variability (eg, weight, type, nicotine content), smoking history (eg, former cigarette smoking), and individual smoking patterns (ie, inhalation behaviors), all of which may have considerable impact on measures of dependence, topography, and nicotine pharmacology. Therefore, it is important to consider these factors when studying dependence in cigar smokers; yet, few studies have done so to date.

Here, we report the results of a clinical study in which adult cigar-only smokers smoked their own brand cigar *ad libitum* for up to one hour following a 24-hour abstinence period. We assessed nicotine dependence, craving and withdrawal symptoms, *ad libitum* smoking topography, and measured biomarkers of exposure following cigar smoking. Importantly, these aims were addressed using a sample stratified for cigar size, former cigarette smoking, and inhalation behaviors, allowing for careful control of these potentially important confounding variables.

METHODS

Participants

Seventy-seven current cigar-only smokers aged 22–77 years (16 females) were recruited from the Albuquerque, NM metropolitan area using advertisements placed throughout the community, in local media, and on clinical trial websites. Databases from prior studies also were culled for potential participants. Participants were study eligible if they were aged 18 years or older, smoked at least one cigar per week for the past 6 months, had not used any other tobacco products within the past 6 months, and were otherwise healthy (based on history and physical exam). Women of child-bearing age were using effective birth control, not breast-feeding, and had a negative urine pregnancy test at screening. Smokers seeking treatment for smoking cessation at the time of study were excluded.

Due to the wide variety of cigar types and use behaviors, participants were stratified according to the following groups to achieve balance in the relative number of participants per group: small cigar versus large cigar smokers; primary versus secondary cigar smokers; and self-reported inhalers versus non-inhalers. The original design of the study classified individuals as small cigar users if their own brand cigar they provided at screening and smoked during the exposure session weighed ≤ 3 grams, and as large cigars users if their own brand cigar weighed >3 grams. Although this definition collapsed small cigars and cigarillos into the same group, during data analysis, we split the small cigar category into small cigars and cigarillos (based on packaging materials and verified by Web searches of cigar brand/subtype) to be more consistent with the existing literature. Primary cigar smokers reported smoking <100 cigarettes in their lifetime, whereas secondary cigar smokers had smoked at least 100 cigarettes in their lifetime. Self-reported inhalers answered: "How often do you inhale cigar smoke?" with "Often" or "Always." Those who responded "Never" or "Sometimes" were classified as self-reported non-inhalers. The original design also planned to stratify based on Hispanic ethnicity and gender; however, enrollment of participants across all 5 stratifications was not feasible and we did not achieve a completely balanced design. Therefore, Hispanic ethnicity and gender were dropped as stratification factors, and used as covariates in all models to improve the marginal balance between factors.

Study Design and Procedures

This study was an unblinded, single-site, single-exposure study seeking to improve understanding of dependence and use behaviors associated with own brand cigar smoking. Participants provided their own brand cigars to use in the study and were reimbursed. The study was conducted between June 2014 and September 2015.

Following a telephone screen to determine eligibility, potential participants were invited to the laboratory for a baseline screening session. After obtaining IRB-approved informed consent, researchers collected vital signs and medical history to determine eligibility. All consented participants provided a urine sample for cotinine and total 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol (NNAL) analyses and completed the demographic surveys, the Hooked on Nicotine Checklist (HONC),²² and the Wisconsin Inventory of Smoking Dependence Motives (WISDM).²³ Participants returned to the study site for the exposure visit following 24 hours smoking abstinence (confirmed by exhaled carbon monoxide (CO) levels ≤ 10 parts per million (ppm)) and brought 2 of their own brand cigars. One cigar was used for nicotine content analysis and the other cigar was smoked *ad libitum* for up to one hour. Participants completed the modified Questionnaire of Smoking Urges – Brief (QSU-B),²⁴ the Minnesota Nicotine Withdrawal Scale (MNWS),²⁵ and a questionnaire to measure perceived health risks before smoking and the QSU-B and MNWS within 30 minutes of smoking completion. Cigars were weighed without filters (when applicable) before and after smoking. Participants were instructed to smoke their own brand cigar as they would normally smoke. Serial plasma samples were collected prior to and 5, 15, 30, 45, 60, 90, and 120 minutes after the initiation of cigar smoking. If blood collection and other measurements were scheduled at the same collection times, blood collection had precedence over other measurements. Vital signs (ie, heart rate, systolic and diastolic blood pressure, temperature, blood oxygen saturation) were collected prior to and at 25, 55, and

115 minutes after the initiation of cigar smoking. Exhaled CO was measured within 2 minutes of smoking completion.

The unsmoked own brand cigars were stored at ambient temperature, away from light and moisture until nicotine analysis. Each cigar was weighed and a portion of the tobacco was removed and ground into a homogenous consistency; nicotine was extracted following the addition of d3-nicotine as the internal standard (IS) using ethyl acetate following 30 minutes of rotation. The sample was centrifuged and supernatant removed for analysis. The extraction process was repeated a total of 3 times. The supernatant was analyzed on an Agilent (Wilmington, DE) 6890N gas chromatograph-mass spectrometer (GC-MS). Nicotine and the IS were chromatographically separated over a 9.5-minute method on a Restek (Bellefonte, PA) RTX-5MS capillary column using helium as the carrier gas (2.3 mL/min) and was detected using single ion monitoring (nicotine: 162 *m/z*, nicotine-d4: 166 *m/z*). The retention time for nicotine was 6.5 minutes and the method had a lower- and upper-limit quantitation of 2 and 30 µg/mL, respectively. The extraction efficiency from tobacco was >90%.

Measures

Participants completed a battery of assessments typically used in cigarette studies but were adapted to cigar smoking; the word “cigarette(s)” was replaced with “cigar(s)” as needed. At the screening visit, following consent, participants completed general demographics and smoking history surveys. The HONC (score range 0–10, higher values indicating greater dependence)²² and the WISDM (subscale scores 1–7, total score 13–91, higher values indicating greater motives for smoking)²³ assessments were also administered at screening. A urine sample was collected for baseline biomarker analysis. On the study day, participants completed the 10-item QSU-B (score range 10–70, higher values indicating greater craving),²⁴ the 7-item MNWS (mean score range 0–4, higher values indicating greater withdrawal symptoms),²⁵ and a questionnaire to assess perceived health risk.

Topography scoring—Smoking sessions were recorded with a Sony HDR-CX220 camcorder; 2 independent raters measured topography for each participant. For each rater, the total number of puffs was tallied and inter-puff interval (IPI) was computed by subtracting the time at which the prior puff ended from the time at which the current puff commenced. A puff start was defined as the point at which the lips were enclosed around the cigar and the end of the cigar turned red; puff end was defined as the point at which the lips were no longer fully enclosing the cigar and the end of the cigar was no longer red. Mean IPI was computed for each participant by rater. Inter-rater reliability had an intra-class correlation coefficient of 0.97.

Biomarkers and physiological measure—Urinary cotinine, the primary nicotine metabolite, and total NNAL were measured in urine samples collected at screening using liquid chromatography mass spectrometry using validated methods. Cotinine concentrations were determined at the Tricore Reference Laboratories (Albuquerque, NM) using an internally developed method with an LOQ of 2 ng/mL and a limit of detection (LOD) of 1 ng/mL. Total NNAL concentrations were determined at the UCSF Tobacco Biomarkers Core

Facility using a modified method based upon previously published work with a limit of quantitation (LOQ) of 0.125 ng/mL.²⁶ Urinary cotinine and total NNAL values were corrected for creatinine concentration: [cotinine (pre)] / ([creatinine (pre)]/100). Venous blood samples were collected with an indwelling catheter to assess plasma nicotine concentrations. Immediately after collection, plasma was separated and frozen at -20°C until analysis. Nicotine concentrations were determined at the Tricore Reference Laboratories (Albuquerque, NM) using an internally developed method with an LOQ of 2 ng/mL and an LOD of 1 ng/mL. When biomarker concentrations were below the LOQ, they were imputed a one-half of the LOD to avoid a bias due to non-detection. The nicotine exposure-related outcomes included plasma nicotine maximum observed concentration ($C_{\max}$), time to maximum concentration ($T_{\max}$), and area under the concentration curve from 0 to 120 minutes (AUC_{0-120}).

Exhaled CO was measured pre-exposure and within 2 minutes of smoking completion with a Vitalograph Breath CO, model 2970 (Lexington, KS; ± 3 ppm accuracy). Exhaled CO (ppm) boost was computed by subtracting the pre-exposure measurement from the post-exposure measurement.

Vital signs including blood pressure (mmHg), heart rate (beats per minute, bpm), respiratory rate (breaths per minute), and oxygen saturation (SpO_2) were collected at screening, pre-exposure and at 25, 55, and 115 minutes post-exposure. An Omron automatic blood pressure monitor, model HEM-705CP, Intelli-sense (Vernon Hill, Illinois) was used for blood pressure and heart rate measurements. Respiratory rate was counted manually.

Data Preparation and Analysis

All data analyses were conducted using R version 3.3.0. Group membership for cigar type (small, cigarillo, or large cigar) was determined by examining packaging materials at the time the cigar was brought to the lab and verified by web searches of the cigar brand/subtype by the first author. Cigarette smoking history and inhalation behavior were designated based on participant responses to the questions mentioned above.

Total scores were computed for the HONC, WISDM, QSU-B, and MNWS using standard methods;²²⁻²⁵ WISDM subscale scores were also calculated.^{23,27} Paired t-tests were used to assess the differences in pre- to post-exposure QSU-B and MNWS scores.

Pharmacokinetic (PK) parameters were determined directly from the data ($T_{\max}$) or were calculated (AUC_{0-120} and $C_{\max}$) using a non-compartmental analysis with linear trapezoidal linear interpolation within Phoenix WinNonlin 6.2 (Certara, Princeton, NJ, USA). $C_{\max}$ and AUC_{0-120} measurements for nicotine were corrected for baseline values according to the following equation: $C_t(\text{adj}) = C_t(\text{obs}) - C_0 \times e^{-kel \cdot t}$, where $C_t(\text{adj})$ is adjusted concentration, $C_t(\text{obs})$ is observed concentration, C_0 is concentration just before smoking, t is time point, and kel is the estimated elimination rate constant based on nicotine's terminal half-life (120 minutes).^{28,29}

Nicotine intake-normalized (I-N) values are also reported based on estimated nicotine intake (consumed weight of cigar (g) $\times$ nicotine concentration of the cigar (mg/g)). Results that

were not normally distributed (plasma nicotine and urinary cotinine, total NNAL) were log transformed prior to statistical analyses. Non-transformed data are presented in the tables, and plasma nicotine values are shown in the figures.

Multiple regression was used for an examination of stratification group (eg, small cigar vs cigarillo vs large cigar) while controlling for other stratifications (eg, primary vs secondary cigar smoker, inhaler vs non-inhaler). Hispanic ethnicity and gender also were included as factors because these aspects were included in the original study design. $p < .05$ was used to determine significance. Of note, whereas multiple regressions were used to determine significance for all between-group tests, the values presented in tables and figures are the raw means and standard deviations for a given group, without any adjustments for the other grouping variables.

RESULTS

Tables 1 shows study participants' demographic data and smoking history. Per the inclusion criteria, all participants were current exclusive cigar users. In multiple regression models, some baseline demographic variables differed within the study groups. Small cigar smokers reported fewer years of cigar smoking than large cigar smokers (Tukey adjusted $p = .02$). In addition, examination of the number of cigars smoked per week revealed differences based on cigar type ($F(2,70) = 15.37$, $p < .001$), cigarette smoking history ($t(70) = 3.00$, $p < .004$), and inhalation behaviors ($t(70) = 2.02$, $p < .05$). Specifically, large cigar and cigarillo smokers smoked fewer cigars than small cigar smokers (both Tukey adjusted $ps < .001$), and secondary cigar smokers and inhalers smoked more cigars per week compared to primary cigar smokers and non-inhalers, respectively.

Cigar Characteristics

Ninety-two percent of small cigar users, 18% of cigarillo users, and 5% of large cigar users reported using a filtered product. Prime Time Large Cigars ($N = 4$) was the most frequently used small cigar brand; Black & Mild ($N = 7$) and Swisher Sweets ($N = 6$) were the most common cigarillo brands, and Acid ($N = 4$) was the most common large cigar brand. No other cigar brands were used by more than 3 participants. On average, small cigars weighed 1.8 g (range: 1.2–3 g) with 4.0 mg nicotine/g tobacco (range: 2.2–6.5 mg/g), cigarillos weighed 2.6 g (range: 0.9–4 g) with 5.5 mg nicotine/g tobacco (range: 2.4–10.3 mg/g), and large cigars weighed an average of 12.0 g (range: 1.6–25 g) with 7.0 mg nicotine/g tobacco (range: 1.3–17.7 mg/g), which was greater than small cigars (Tukey adjusted $p < .05$) and marginally greater than cigarillos (Tukey adjusted $p = .10$).

Nicotine Dependence

Table 2 reports the average total HONC and WISDM scores. There was a statistically significant effect of cigar type on HONC scores ($F(2, 66) = 3.98$, $p < .03$). In addition, secondary cigar smokers had higher scores than primary cigar smokers ($t(66) = 2.64$, $p = .01$), and inhalers had significantly higher scores than non-inhalers ($t(66) = 3.98$, $p < .001$), when controlling for the other factors. WISDM total scores only differed among inhalers and

non-inhalers ($t(67) = 2.87, p < .01$). In addition, 3 of the 4 dependence-related WISDM subscales showed statistically significant group differences (Table 2).

Craving/Withdrawal

Table 2 reports pre- and post-exposure total QSU-B and MNWS scores. After *ad libitum* smoking, total QSU-B and MNWS scores decreased significantly ($t(76) = 8.66, p < .0001$ and $t(76) = 5.37, p < .0001$ respectively).

There were baseline differences in QSU-B scores based on cigar type ($F(2, 70) = 6.91, p < .002$) and inhalation behavior ($t(70) = 4.07, p < .001$), and baseline MNWS scores also differed across cigar type ($F(2,70) = 4.97, p < .01$) and inhalation behavior ($t(70) = 2.65, p = .01$). Comparisons of craving and withdrawal by group revealed significantly greater reductions from baseline to post-cigar exposure in inhalers compared to non-inhalers for the QSU-B ($t(70) = 3.26, p = .002$) and MNWS ($t(70) = 2.79, p < .007$). Table 2 shows group means (SD) and a summary of statistically significant findings.

Use Behavior

As expected, there was a statistically significant effect of cigar type on tobacco consumed ($F(2, 70) = 38.36$), such that large cigar smokers consumed more tobacco (by weight) than small cigar and cigarillo smokers (Tukey adjusted $ps < .0001$; Figure 1), when controlling for the other groups. On average, large cigar smokers consumed 51% (range: 14%–87%), small cigar smokers consumed 63% (range: 18%–78%), and cigarillo smokers consumed 58% (range: 15%–84%) of their cigars. Cigar nicotine concentration and the difference in cigar weight after smoking were used to estimate nicotine intake (consumed weight of cigar (g) / nicotine concentration (mg/g)). Estimated nicotine intake differed as a function of cigar type ($F(2, 70) = 31.06, p < .001$), such that large cigar smokers had significantly greater intake than small and cigarillo smokers (both Tukey adjusted $ps < .001$); no other group differences emerged.

Video-recorded smoking topography measurements (Table 3) were collected for 75 participants and included smoking duration, puff number, and IPI. Analyses revealed significant effects of cigar type on total smoking duration ($F(2,70) = 29.61, p < .001$), number of puffs ($F(2,68) = 29.72, p < .001$), puff duration ($F(2,68) = 7.37, p = .001$), and IPI ($F(2,68) = 7.12, p = .002$). In addition, there were statistically significant effects of cigarette smoking history on smoking duration ($t(70) = 2.44, p = .02$) and puff duration ($t(68) = 2.10, p = .04$).

Biomarkers of Exposure

At screening, urinary cotinine and total NNAL levels were highly variable among all participants and within groups (Table 4). Using multiple regression models, primary cigar smokers had significantly lower cotinine ($t(70) = 6.36, p < .001$) and total NNAL ($t(68) = 6.64, p < .001$) concentrations than secondary cigar smokers; no other effects emerged between the groups.

At the exposure visit, the majority of participants' baseline exhaled CO levels were 10 ppm, indicative of 24 hours smoking abstinence. Two participants had baseline CO >10 ppm, but both had nicotine levels 4 ng/mL, indicative of smoking abstinence, and thus, were included in all analyses. Immediately following cigar smoking, exhaled CO levels increased significantly in all groups, including self-reported non-inhalers. As expected, exhaled CO boost was significantly greater in secondary cigar smokers compared to primary cigar smokers ($t(70) = 3.00$, $p = .004$) and in inhalers compared to non-inhalers ($t(70) = 4.88$, $p < .001$) in multiple regression analyses (Figure 2).

Nicotine exposure following *ad libitum* cigar smoking was highly variable (Table 4). The plasma nicotine concentration-time curves for all groups are shown in Figure 3. Examination of log transformed nicotine $C_{\max}$ values revealed effects of cigar type ($F(2,66) = 5.31$, $p = .007$) and inhalation behaviors ($t(66) = 3.00$, $p = .004$): large cigar smokers and inhalers had greater nicotine $C_{\max}$ than small cigar smokers and non-inhalers, respectively (Tukey adjusted $p = .01$). Similarly, large cigar smokers and inhalers had greater nicotine AUC than small cigar smokers ($F(2,66) = 5.61$, $p = .006$) and non-inhalers ($t(66) = 3.03$, $p = .004$), respectively (Table 4).

To evaluate the efficiency of nicotine delivery, nicotine $C_{\max}$ and AUC_{0-120} were normalized based on estimated nicotine intake (intake normalized; I-N). Contrary to findings from non-normalized data, large cigar smokers had significantly lower I-N $C_{\max}$ than both small cigar smokers (Tukey adjusted $p < .04$) and cigarillo smokers (Tukey adjusted $p < .005$). Secondary cigar smokers had greater concentrations than primary cigar smokers ($t(66) = 2.31$, $p < .03$) and inhalers also showed greater peak nicotine I-N concentrations than non-inhalers ($t(66) = 3.08$, $p = .003$). There was also a significant effect of cigar type on nicotine I-N AUC_{0-120} ($F(2,66) = 5.90$, $p < .005$), with cigarillo smokers having larger nicotine I-N AUC_{0-120} values than large cigar smokers (Tukey adjusted $p = .008$). Nicotine I-N AUC_{0-120} results were similar to non-normalized data. We also normalized based on the total amount of estimated tobacco consumed. Table 4 presents these results. Of note, tobacco normalized results were nearly identical to the results using I-N values.

Nicotine $T_{\max}$ (mean (SD)/median) was generally achieved after smoking was completed, and was significantly different between inhalers (43.6 (31.0)/30 mins) and non-inhalers (69.9 (36.2)/60 mins; $p = .002$) and marginally different between primary (65.9 (35.0)/60 min) and secondary (52.1 (36.5)/45 mins) cigar smokers. There were no significant differences in $T_{\max}$ based on cigar type ($p = .24$).

Physiological Effects

Table 5 reports the monitored physiological effects. Compared to baseline measurements, cigar smoking significantly increased heart rate ($t(76) = 4.41$, $p < .0001$), diastolic ($t(76) = 7.62$, $p < .0001$) and systolic ($t(76) = 8.89$, $p < .0001$) blood pressures, respiratory rate ($t(76) = 5.58$, $p < .0001$), and SpO_2 ($t(76) = 5.99$, $p < .0001$). In multiple regression analyses, secondary cigar smokers had smaller reductions in SpO_2 compared to primary cigar smokers ($t(70) = 2.09$, $p = .04$); no other effects emerged. Anticipated adverse events included dizziness and lightheadedness. There were no un-anticipated or serious adverse events reported during the study.

DISCUSSION

We examined several behavioral indices and biomarkers of cigar smoking in participants stratified based on cigar size (large vs cigarillo vs small cigars), cigarette smoking history (primary vs secondary cigar smokers), and self-reported inhalation behaviors (inhaler vs non-inhaler). We examined nicotine dependence and the impact of *ad libitum* cigar smoking on craving and withdrawal symptoms and nicotine pharmacology. As a result, we have advanced the understanding of how cigar type and smoking behaviors impact nicotine dependence and exposure.

Nicotine Dependence

Overall, participants showed low to moderate levels of loss of autonomy over cigar use, as measured by the HONC, with scores ranging from 0 to 10, although the mean score was lower than in prior reports of cigarette smokers.²² Our data suggest that this variability may be primarily driven by inhalation behaviors. Greater dependence in inhalers is not particularly surprising because inhalers may have enhanced nicotine bioavailability due to the large surface area of the lung,³⁰ thereby increasing the likelihood of experiencing nicotine's pharmacological effects and subsequent necessity to smoke cigars.

Also indicative of low to moderate levels of dependence, most participants experienced mild craving and withdrawal symptoms following 24-hour abstinence. Although these scores were lower than those reported in prior studies of similarly-abstinent cigarette smokers,^{31,32} similar symptoms have been reported in cigarillo smokers upon overnight abstinence.¹⁰ In addition, a cross-sectional survey analysis revealed that cigar-only smokers exhibit some symptoms of nicotine dependence, including craving tobacco.³³

Cigar smoking significantly reduced QSU-B and MNWS scores, as previously reported,^{8,10,11} suggesting that cigar smoking confers some benefit for reducing the negative symptoms associated with withdrawal.

Use Behaviors

Although the measures of smoking topography included in the current study were somewhat limited compared to reports utilizing automated topography devices,^{8,10} results still elucidate important group differences. As expected, we found significant differences in *ad libitum* smoking topography based on cigar type. Not only did large cigar smokers smoke longer, they also smoked more tobacco and were exposed to a greater estimated nicotine intake than small cigar and cigarillo smokers. It should be noted that the shorter IPI in large cigar smokers may be a result of multiple mini puffs in sequence before a longer puff. However, topography among cigar smokers (and within a cigar type) was highly variable, highlighting a distinct challenge for developing standardized smoking methods that accurately predict delivery of nicotine and other constituents from cigars.

Biomarkers of Exposure

We found that exclusive cigar smokers who smoke at least one cigar per week have measurable urinary cotinine and total NNAL concentrations, although levels varied among

participants. Upon smoking a single own brand cigar, plasma nicotine levels increased significantly overall and within each group. The increases in plasma nicotine concentrations we observed in exclusive small cigar and cigarillo smokers are similar to, or lower than, those previously reported for *ad libitum* use of cigarillos.^{10,12,20} One study with *ad libitum* large cigar smoking also reported similar increases in plasma nicotine concentrations as reported here.¹¹

Any differences between these studies and our results may be due to different use behaviors (ie, inhalation) and/or nicotine dependence in exclusive cigar smokers with 24 hour abstinence (present study) compared to dual users with no required abstinence.^{8,11,12} Indeed, we found that inhalation behavior significantly affects $C_{\max}$ and AUC_{0-120} .

A prior report suggests that secondary cigar smokers may be more likely to inhale cigar smoke due to their history of inhaling cigarette smoke.³⁴ Although we did find that cigarette smoking history tended to impact nicotine pharmacology, we also report that inhalation behaviors significantly influence nicotine intake-normalized pharmacokinetic parameters (I-N $C_{\max}$ and I-N AUC_{0-120}), indicating greater nicotine bioavailability through smoke inhalation. Our results are similar to studies that found that non-inhalers and primary cigar smokers had lower nicotine exposures than inhalers and secondary cigar smokers.^{21,35}

By comparing self-reported inhalation behaviors with exhaled CO levels, our results extend beyond self-report measures. Importantly, we found that exhaled CO levels significantly increased following cigar smoking in all groups. These findings confirm previous reports in dual cigar and cigarette smokers,^{8-10,12,20,36} suggesting that many cigar smokers are exposed to significant levels of CO. Importantly, even self-reported non-inhalers had small, yet significant, increases in exhaled CO, perhaps indicative of mild smoke inhalation. We also found that primary cigar smokers had smaller exhaled CO boosts compared to secondary cigar smokers, indicating that former cigarette smoking may impact cigar smoke inhalation, as previously observed.³⁵

Physiological Effects

Ad libitum cigar smoking induced significant physiological changes as observed with other tobacco products.^{19,20,36,37} We found that cigar smoking increased heart rate and both systolic and diastolic blood pressure, as previously reported in cigar smokers.^{18-20,36} Therefore, cigar smoking, as with cigarette smoking, induces rapid physiological effects on the cardiovascular system.

Limitations

The experimental design (*ad libitum* smoking of own brand cigar) led to variability in all outcome measures. Despite the variability, we observed significant differences in dependence, topography, and nicotine exposure as a function of cigar type, cigarette smoking history, and self-reported inhalation behavior, highlighting the importance of examining these cigar and user characteristics in future clinical studies with cigar smokers.

Whereas our study is the first to determine the impact of cigar type, cigarette smoking history, and inhalation behaviors on dependence, topography, and nicotine exposure, it has

limitations. We did not account for the presence of filters or flavors that may impact use behaviors. Moreover, due to participant demographics and study design (equal recruitment into use behavior groups), our results are not nationally representative. For example, nationally representative estimates from 2015 indicate that over one million youth (under the age of 18) smoke cigars.³⁸ In the current study, our participants reported initiating cigar smoking much later, on average, at age 28. Due to the relationship between age of initiation and nicotine dependence,³⁹ our results may underestimate nicotine dependence among some cigar smokers. Furthermore, study participants were exclusive cigar smokers, but other reports suggest that many cigar smokers also smoke cigarettes or use other tobacco products,³⁹ which may impact nicotine dependence.³³

Although few in number, women who were using oral contraceptives were included in the study, and these drugs' effects on nicotine metabolism may have affected biomarker outcomes.⁴⁰ Next, our nicotine-intake normalized exposure estimates do not account for participants' puff topography or cigar smoke yields, and therefore, may overestimate actual intake. Finally, because our study assessed smoking behaviors with own brand cigars of various sizes, we were unable to use standard topography devices; our smoking topography data were scored by independent reviewers and video recordings.

This was not a randomized study and between-group comparisons should be interpreted with caution. Furthermore, the current study included many different dependent variables, and statistical analyses were not corrected for multiple comparisons.

IMPLICATIONS FOR TOBACCO REGULATION

To protect public health, the FDA's Center for Tobacco Products now has regulatory authority over all cigars under the Family Smoking Prevention and Tobacco Control Act. As a part of this "deeming" rule, the FDA is able to prevent misleading claims, ensure that the products allowed on the market meet statutory requirements to protect public health, and continue public education campaigns. Our study begins to describe how cigar type and smoking behaviors impact dependence and nicotine exposure in exclusive cigar smokers; these findings may serve to further inform FDA, public education campaigns, and consumers about the risks of cigar smoking. Importantly, this research underscores the importance of mitigating the effects of cigar smoking on the public's health by promoting tobacco prevention and control interventions focused on all tobacco products.

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Figure 1.

Estimated Nicotine Intake and Tobacco Consumption

Note.

Boxplots present the total amount of tobacco consumed (a,c,e), defined as the baseline cigar weight – post-exposure cigar weight, and the total intake of nicotine (b,d,e) across the 3 study stratifications (small cigars vs cigarillos vs large cigars; cigarette smoking history; inhaler vs non-inhaler). The boxplots show the median (solid horizontal line), the 25th and 75th percentile (bottom and top of box), and the range of relevant variables that

approximates the 95% confidence interval (whiskers). Points outside this range (circles) represent outliers.

Figure 2.

Increases in CO from Baseline to Post-exposure during the Ad Libitum Session

Note.

Boxplots present the total change in CO (post-exposure – baseline) across each of the 3 study stratifications (small cigars vs cigarillos vs large cigars; cigarette smoking history; inhaler vs non-inhaler). The boxplots show the median (solid horizontal line), the 25th and 75th percentile (bottom and top of box), and the range of relevant variables that approximates the 95% confidence interval (whiskers). Points outside this range (circles) represent outliers.

Figure 3.

Plasma Nicotine Levels during the Ad Libitum Cigar Smoking Session

Note.

Plots show plasma nicotine levels across each of the 3 study stratifications (small cigars vs cigarillos vs large cigars; cigarette smoking history; inhaler vs non-inhaler). Displayed are means and standard error of the mean for each timepoint collected in the study.

Table 1

Study Participants' Demographics and Smoking History

	Cigar Type			Cigarette Smoking History			Self-reported Inhalation Behaviors	
	All	Small	Cigarillo	Large	Primary	Secondary	Inhaler	Non-inhaler
N	77	13	22	42	35	42	36	41
Age, Mean (SD)	50.2 (14.3)	47.0 (14.9)	49.2 (13.8)	51.5 (14.5)	47.2 (13.9)	52.8 (14.3)	49.6 (13.2)	50.8 (15.2)
% Male	78.0	46.2	86.4	83.3	80.0	76.2	76.5	79.1
% Hispanic	39	30.8	18.2	52.4	45.7	33.3	29.4	46.5
Age at First Cigar Use, Mean (SD)	28.0 (14.2)	26.2 (16.6)	29.8 (15.6)	27.6 (12.9)	26.9 (12.8)	29.0 (15.4)	28.7 (15.1)	27.5 (13.6)
Age at Regular Cigar Use, Mean (SD)	37.4 (14.2)	40.4 (17.0)	39.8 (12.9)	35.3 (13.9)	34.1 (12.7)	40.2 (14.9)	37.1 (15.8)	37.7 (12.9)
Years Regular Cigar Smoker, Mean (SD)	11.8 (11.6)	5.2 (5.4) ^c	9.2 (6.7)	15.2 (13.8) ^a	11.8 (11.8)	11.8 (11.6)	11.3 (13.2)	12.1 (10.3)
# Cigars/Week, Mean (SD)	18.7 (35.2)	58.9 (66.3) ^{b,c}	19.4 (21.0) ^a	6.0 (8.0) ^a	8.2 (13.7) [*]	27.5 (44.2) [*]	27.4 (45.1) [#]	11.9 (23.2) [#]
% Making at Least One Quit Attempt	17	31	14	14	20	14	18	16
Perceived Health Risks	0.28 (0.20)	0.45 (0.21) ^{b,c}	0.26 (0.21) ^a	0.23 (0.17) ^a	0.26 (0.19)	0.29 (0.21)	0.36 (0.23) [#]	0.21 (0.15) [#]

Note.

Group means (SD) presented in the table represent the mean of the particular group without respect to the other group classifications. Perceived Health Risk scores are on a scale from 0 to 1, where a score of 0 represents a perceived health risk that cigars are much less risky than cigarettes and 1 represents a perceived health risk that cigars are much more risky than cigarettes. Statistically significant differences ($p < .05$) for Cigar Type are denoted with superscripts showing the relative group differences where ^a = Small, ^b = Cigarillo, and ^c = Large; all follow-up comparisons are corrected for multiple comparisons using Tukey's method for multiple comparisons (Tukey adjusted $ps < .05$).

* Statistically significant differences ($p < .05$) between primary and secondary cigar smokers.

Significant differences ($p < .05$) between self-reported Inhalers and Non-inhalers.

Table 2

Dependence and Craving/Withdrawal Measures in Cigar Smokers

	Cigar Type			Cigarette Smoking History			Self-reported Inhalation Behaviors	
	All	Small	Cigarillo	Large	Primary	Secondary	Inhaler	Non-inhaler
HONC	2.8 (2.8)	4.8 (3.1) ^c	3.0 (3.1)	2.1 (2.1) ^a	2.0 (2.7) [*]	3.4 (2.7) [*]	4.1 (3.2) [#]	1.8 (1.9) [#]
WISDM, Total	34.0 (12.1)	40.6 (16.2)	31.3 (9.7)	33.2 (11.3)	32.8 (11.8)	35.0 (12.5)	38.3 (12.2) [#]	30.5 (11.0) [#]
Automaticity	2.2 (1.4)	3.0 (1.7)	2.0 (1.0)	2.0 (1.4)	1.9 (1.2)	2.4 (1.5)	2.5 (1.6)	1.9 (1.2)
Loss of Control	2.0 (1.3)	2.9 (1.6) ^c	2.0 (1.3)	1.7 (1.0) ^a	1.8 (1.2)	2.2 (1.3)	2.4 (1.4) [#]	1.7 (1.1) [#]
Craving	2.5 (1.5)	4.1 (1.7) ^{b,c}	2.4 (1.4) ^a	2.1 (1.2) ^a	2.3 (1.4)	2.7 (1.5)	3.1 (1.6) [#]	2.0 (1.2) [#]
Tolerance	2.4 (1.6)	3.5 (2.0) ^c	2.5 (1.6)	1.9 (1.3) ^a	1.8 (1.3) [*]	2.8 (1.7) [*]	3.0 (1.6) [#]	1.9 (1.4) [#]
QSU-Brief, Baseline	26.6 (14.4)	38.8 (18.1) ^{b,c}	25.5 (12.3) ^a	23.5 (12.5) ^a	24.2 (12.9)	28.7 (15.4)	33.3 (15.3) [#]	21.4 (11.4) [#]
QSU-Brief, Post-exposure	16.2 (8.9)	24.0 (12.6)	13.5 (4.3)	15.1 (8.1)	15.2 (7.5)	17.0 (9.9)	18.6 (9.6)	14.3 (7.9)
QSU-Brief, Absolute Change	10.5 (10.6)	14.8 (11.1)	12.0 (10.1)	8.4 (10.5)	9.1 (10.3)	11.7 (10.8)	14.8 (11.8) [#]	7.1 (8.2) [#]
MINWS, Baseline	0.8 (0.9)	1.5 (1.1) ^{b,c}	0.7 (0.7) ^a	0.7 (0.8) ^a	0.9 (0.9)	0.8 (0.9)	1.1 (1.0) [#]	0.6 (0.7) [#]
MINWS, Post-exposure	0.5 (0.6)	0.8 (0.8)	0.5 (0.6)	0.3 (0.5)	0.5 (0.6)	0.4 (0.6)	0.5 (0.7)	0.4 (0.6)
MINWS, Absolute Change	0.4 (0.6)	0.7 (0.7) ^b	0.1 (0.5) ^a	0.4 (0.6)	0.4 (0.7)	0.4 (0.5)	0.6 (0.7) [#]	0.2 (0.5) [#]

Note.

Group means (SD) presented in the table represent the mean of the particular group without respect to the other group classifications (ie, the mean of 2.1 for the HONC total score for the Large group represents the HONC total score for all individuals who smoked large cigars). Automaticity, Loss of Control, Craving, and Tolerance are 4 WISDM subscales that represent dependence motives. Significant differences ($p < .05$) for Cigar Type are denoted with superscripts showing the relative group differences where ^a = Small, ^b = Cigarillo, and ^c = Large; all follow-up comparisons are corrected for multiple comparisons using Tukey's method for multiple comparisons (Tukey adjusted $ps < .05$).

* Statistically significant differences ($p < .05$) between primary and secondary cigar smokers.

Statistically significant differences ($p < .05$) between self-reported Inhalers and Non-inhalers.

Table 3*Ad Libitum* Cigar Smoking Topography

	All	Cigar Size			Cigarette Smoking History			Self-reported Inhalation Behaviors	
		Small	Cigarillo	Large	Primary	Secondary	Inhaler	Non-inhaler	
Smoking Duration (min)	30.2 (18.9)	9.9 (4.2) ^c	20.8 (9.5) ^c	41.4 (17.4) ^{a,b}	34.5 (19.1) [*]	26.7 (18.2) [*]	27.5 (18.8)	32.4 (18.9)	
Puff Number	75.5 (59.5)	24.5 (13.3) ^c	35.3 (17.8) ^c	112.3 (57.1) ^{a,b}	84.3 (58.9)	68.3 (59.7)	75.1 (69.5)	75.8 (51.2)	
Puff Duration (sec)	1.4 (0.6)	1.8 (0.7) ^c	1.6 (0.6) ^c	1.2 (0.4) ^{a,b}	1.3 (0.5) [*]	1.5 (0.7) [*]	1.4 (0.6)	1.4 (0.6)	
IPI¹ (sec)	26.7 (14.1)	24.3 (7.8) ^b	35.8 (16.1) ^{a,c}	22.7 (12.6) ^b	25.4 (13.1)	27.7 (14.9)	24.8 (11.2)	28.2 (16.0)	
Estimated I-N (mg)	25.5 (25.2)	4.8 (2.6) ^c	8.3 (4.8) ^c	40.9 (25.1) ^{a,b}	28.8 (24.7)	22.7 (25.6)	23.4 (24.7)	27.2 (25.8)	

Note.

Group means (SD) presented in the table represent the mean of the particular group without respect to the other group classifications.

¹ IPI = interpuff interval.Statistically significant differences ($p < .05$) for Cigar Type are denoted with superscripts showing the relative group differences where ^a = Small, ^b = Cigarillo, and ^c = Large; all follow-up comparisons are corrected for multiple comparisons using Tukey's method for multiple comparisons (Tukey adjusted $ps < .05$).^{*} Statistically significant differences ($p < .05$) between primary and secondary cigar smokers.[#] Statistically significant differences ($p < .05$) between self-reported Inhalers and Non-inhalers.

Table 4

Biomarkers of Exposure Associated with *Ad Libitum* Cigar Smoking

	Cigar Size			Cigarette Smoking History			Self-reported Inhalation Behaviors	
	All	Small	Large	Primary	Secondary	Inhaler	Inhaler	Non-inhaler
Screening Visit								
Cotinine	469.0 (802.3)	640.4 (783.8)	695.2 (1024.6)	87.3 (186.9) [*]	787.1 (967.5) [*]	657.5 (924.9)	320.0 (664.2)	
Total NNAL	418.3 (712.2)	859.0 (1167.7)	552.7 (794.2)	84.2 (169.2) [*]	680.7 (856.1) [*]	665.2 (961.1)	213.5 (285.6)	
Exposure Visit								
Baseline Plasma Nicotine	0.7 (0.9)	0.6 (0.4)	0.8 (1.4)	0.5 (0.0)	0.9 (1.2)	0.9 (1.2)	0.6 (0.5)	
Nicotine C _{max}	10.2 (10.5)	5.8 (5.7) ^c	8.2 (7.1)	8.4 (9.8)	11.7 (11.0)	13.2 (12.3) [#]	7.9 (8.5) [#]	
Range	0.3 – 54.7	0.3 – 17.6	0.3 – 25.6	0.3 – 54.7	0.3 – 54.7	0.3 – 54.7	0.3 – 37.7	
Nicotine AUC ₀₋₁₂₀	742.3 (870.4)	343.6 (299.1) ^c	601.0 (559.9)	613.1 (769.1)	848.8 (942.0)	989.7 (1093.6) [#]	549.1 (591.2) [#]	
Range	12.2 – 5252.5	12.2 – 921.6	17.2 – 2044.3	27.8 – 5262.5	12.2 – 3367.7	17.5 – 5262.5	12.2 – 2844.2	
I-N Nicotine C _{max}	0.8 (1.3)	1.3 (1.3) ^c	1.3 (2.0) ^c	0.4 (0.4) [*]	1.2 (1.7) [*]	1.3 (1.7) [#]	0.5 (0.6) [#]	
I-N Nicotine AUC ₀₋₁₂₀	56.7 (91.8)	75.3 (64.0)	99.3 (148.8) ^c	29.0 (35.4) [*]	79.5 (115.6) [*]	88.9 (124.6) [#]	31.4 (40.6) [#]	
T-N Nicotine C _{max}	4.1 (6.0)	4.9 (4.7)	6.7 (9.5) ^c	2.3 (2.2) [*]	5.5 (7.6) [*]	6.1 (8.1) [#]	2.4 (2.8) [#]	
T-N Nicotine AUC ₀₋₁₂₀	287.5 (440.3)	285.3 (228.7)	494.8 (713.5)	166.9 (183.9)	386.9 (554.7)	439.7 (599.4)	168.6 (193.6)	

Note.

Group means (SD) presented in the table represent the mean of the particular group without respect to the other group classifications. I-N = Nicotine Intake (consumed weight of cigar (g) × nicotine concentration (mg/g)). Units for Urinary Cotinine and Total NNAL: ng/mg creatinine. Nicotine C_{max} and I-N Nicotine C_{max}: ng/mL; NicotineAUC₀₋₁₂₀ and I-N Nicotine AUC₀₋₁₂₀: min × ng/mL. T-N Nicotine C_{max}: C_{max} normalized by the amount of tobacco smoked (ie, ng/mL/g tobacco). I-N Nicotine AUC: AUC normalized by the amount of tobacco smoked (ie, min × ng/mL/g tobacco).

Statistically significant differences (p < .05) for Cigar Type are denoted with superscripts showing the relative group differences where ^a = Small, ^b = Cigarillo, and ^c = Large; all follow-up comparisons are corrected for multiple comparisons using Tukey's method for multiple comparisons (Tukey adjusted ps < .05).

^{*} Statistically significant differences (p < .05) between primary and secondary cigar smokers.

[#] Statistically significant differences (p < .05) between self-reported Inhalers and Non-inhalers.

Table 5Physiological Changes Associated with *Ad Libitum* Cigar Smoking – Mean (SD)

	All	Cigar Size			Cigarette Smoking History			Self-reported Inhalation Behaviors		
		Small	Cigarillo	Large	Primary	Secondary	Inhaler	Non-inhaler		
Heart Rate (bpm)	4.8 (9.6)	1.0 (7.2)	3.9 (9.4)	6.5 (10.1)	2.9 (10.2)	6.5 (8.9)	5.7 (9.6)	4.1 (9.6)		
Diastolic BP (mmHg)	6.8 (7.8)	3.6 (7.1)	6.0 (9.2)	8.2 (7.0)	6.8 (8.2)	6.8 (7.6)	6.2 (8.3)	7.2 (7.5)		
Systolic BP (mmHg)	12.1 (11.9)	10.6 (7.0)	12.5 (8.6)	12.3 (14.5)	11.7 (12.8)	12.4 (11.3)	12.5 (11.6)	11.8 (12.3)		
Respiratory Rate	1.8 (2.9)	0.6 (0.9)	2.2 (3.9)	2.0 (2.6)	1.8 (2.7)	1.8 (3.0)	2.0 (3.4)	1.7 (2.4)		
SpO₂	1.4 (2.1)	1.4 (1.7)	1.6 (2.0)	1.3 (2.3)	2.0 (2.3) *	1.0 (1.8) *	1.4 (2.2)	1.5 (2.1)		

Note.

Group means (SD) presented in the table represent the mean of the particular group without respect to the other group classifications. Numbers reported are boosts in relevant physiological measure from baseline to post-exposure.

* Statistically significant differences ($p < .05$) between primary and secondary cigar smokers.