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BMJ Open

Triangulating abuse liability assessment for flavoured cigar products using physiological, behavioural economic and subjective assessments: a within-subjects clinical laboratory protocol

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ABSTRACT

Introduction In the USA, Food and Drug Administration regulations prohibit the sale of flavoured cigarettes, with menthol being the exception. However, the manufacture, advertisement and sale of flavoured cigar products are permitted. Such flavourings influence positive perceptions of tobacco products and are linked to increased use. Flavourings may mask the taste of tobacco and enhance smoke inhalation, influencing toxicant exposure and abuse liability among novice tobacco users. Using clinical laboratory methods, this study investigates how flavour availability affects measures of abuse liability in young adult cigarette smokers. The specific aims are to evaluate the effect of cigar flavours on nicotine exposure, and behavioural and subjective measures of abuse liability.

Methods and analyses Participants (projected n=25) are healthy smokers of five or more cigarettes per day over the past 3 months, 18–25 years old, naive to cigar use (lifetime use of 50 or fewer cigar products and no more than 10 cigars smoked in the past 30 days) and without a desire to quit cigarette smoking in the next 30 days. Participants complete five laboratory sessions in a Latin square design with either their own brand cigarette or a session-specific Black & Mild cigar differing in flavour (apple, cream, original and wine). Participants are single-blinded to cigar flavours. Each session consists of two 10-puff smoking bouts (30 s interpuff interval) separated by 1 hour. Primary outcomes include saliva nicotine concentration, behavioural economic task performance and response to various questionnaire items assessing subjective effects predictive of abuse liability. Differences in outcomes across own brand cigarette and flavoured cigar conditions will be tested using linear mixed models.

Ethics and dissemination The Virginia Commonwealth University Institutional Review Board approved the study (VCU IRB: HM20007848). Dissemination channels for study findings include scientific journals, scientific meetings, and policy briefs.

Trial registration number NCT02937051.

Strengths and limitations of this study

- This study will provide the opportunity to examine the abuse liability across flavours of one of the most popular cigar brands in a population that is at increased risk of harm from flavoured tobacco products.
- The study triangulates abuse liability assessment in a clinical laboratory setting using physiological, behavioural and subjective measures.
- Use of behavioural economic tasks to measure abuse liability for cigars represents a novel approach to understand this tobacco product type.
- As this study is being conducted in a controlled setting at a single site, results may not generalise to other use conditions/settings or among other populations/geographic regions.

INTRODUCTION

In 2009, the US Food and Drug Administration (FDA) banned cigarettes with characterising flavours (except for menthol[1]), given their appeal to youth.[2] Five years later, the FDA proposed broader regulatory authority over cigars but did not restrict the availability of flavoured cigars.[3] However, in March 2018, an Advanced Notice of Proposed Rulemaking was issued by the FDA, in which commentary and research are sought to inform the regulation of flavours in tobacco products including cigars.[4] These ongoing changes in tobacco regulation and the evolution of the tobacco marketplace highlight the need for empirical evidence regarding the use and appeal of cigar products and their associated flavours.

The availability of flavours for cigars, among other product characteristics, has been linked to increased cigar sales[5] and consumption.[6] These increases are greatest among youth/

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young adults.[2 7 8] In 2012–2013, 7.3% of US adults smoked cigars every day or some days,[9] and 12.6% of high school students reported past month use.[10] The vast majority (nearly 90%) of youth/young adult cigar smokers report usual brands that offer flavoured varieties.[2] Black & Mild (B&M) is the most popular brand among cigar smokers, offering at least eight flavoured varieties[11] and, accordingly, a much greater proportion of 12–17-year-old cigar users (51%) prefer B&M compared with those 35 or older (18%).[2] The range of flavoured cigars is vast and includes flavours that are fruit-like (Apple, Peach), food/dessert-like (Cream, Dulce de Leche), alcohol-like (Wine, Double Barrel Rum) and unlike anything normally associated with gustatory or olfactory sensation (Jazz, Diamonds)[11 12]; fruit, sweet/candy and wine are the most popular flavours.[2 13 14] Evidence from tobacco industry documents and epidemiological work suggests that such flavour additives are used to promote appeal among novice users[15–17] as well as to mask the taste of tobacco and enhance smoke inhalation.[18] Additionally, a strong literature supports the role of flavours in influencing positive perceptions, and ultimately use, of tobacco products including cigars.[2 19–22] Flavoured cigar use among youth is also associated with lower intentions to quit compared with youth who use non-flavoured tobacco products.[23] In tandem with cigar flavours, factors like marketing and price may promote initiation and continued use.[7 17 24] For example, B&Ms are defined by weight (more than 3 lbs/1000) in the USA as large cigars via tax guidelines[11] and thus are much cheaper than some other cigar subtypes. Together, these factors combine to make cigars appealing, suggesting the need to better understand the extent to which flavours influence the potential for initiation and subsequent use of cigars.

Clinical laboratory methods provide an important means to understand how flavour may influence tobacco product use patterns and abuse liability. Generally, abuse liability is the degree to which a psychoactive drug or formulation would be used for non-medical purposes and abuse of that drug would lead to physical or psychological dependence.[25] With respect to tobacco products, abuse liability refers to the likelihood that a given product's reinforcement value will lead to persistent use and dependence.[26] The clinical laboratory setting allows for systematic, efficient assessment of physiological effects (eg, nicotine and toxicant exposure, cardiovascular response), behavioural choice tasks and subjective responses,[27] all of which are important for predicting tobacco use patterns including the likelihood for progression to regular use, potential for harm[28] and abuse liability.[24–26] For example, among regular B&M cigar smokers, completing two 10-puff bouts of an active (lit) B&M yielded significantly greater nicotine exposure, heart rate, expired air carbon monoxide (CO) and positive subjective effects compared with two 10-puff bouts of an unlit B&M (sham).[29] However, relative to combustible tobacco cigarettes (CTCs), B&M cigars appear to deliver less nicotine per puff and produce higher CO exposure and greater smoke volume in both primarily CTC and primarily cigar smokers.[29–32] In terms of subjective measures, B&Ms may produce acute positive subjective effects (ie, increased ratings of 'satisfying,' 'calm you down') as well as those indicative of drug effects (increased ratings of 'dizzy'),[29 30] but the only existing direct comparison of subjective effects between cigarettes and cigars (performed among dual users of cigarettes and cigars) suggests that cigarettes are more effective at reducing the craving to smoke.[33] Behavioural choice tasks such as the cigarette purchase task and multiple choice procedure assess abuse liability by measuring how hypothetical or potentially real consumption of tobacco products changes in response to the price of these products,[34–38] providing evidence on how reinforcing these products are. These behavioural choice tasks have not been used to assess cigars and, importantly, no studies have controlled for the influence of cigar flavour on any of the above outcomes in the clinical laboratory. Flavours could affect cigar appeal among novice users,[15–17] and increase cigar smoke inhalation,[18] leading to increased nicotine exposure and subsequent continued use. As previous work from our team[39] and others[40 41] supports, simultaneously assessing physiological, behavioural and subjective measures in the clinical laboratory allows efficient and cost-effective testing of all of these hypotheses.

Considering the current tobacco marketplace and increasing rates of cigar use among vulnerable populations,[2 7 8] evaluating the effects of cigar flavours on abuse liability is essential to protecting public health and informing FDA regulation of cigars. Clinical laboratory methods are uniquely suited to measure the effects of cigar flavours on abuse liability by using a controlled setting to provide much-needed data. Our research uses an innovative approach and includes key advances to improve our understanding of how cigar flavours may influence use. These innovations include: (1) testing the most popular cigar brand and flavours, (2) triangulating abuse liability in the laboratory using physiological, behavioural and subjective measures and (3) purposeful accrual of a population at increased risk of harm from flavoured cigar products (ie, young adult cigarette smokers). The specific aims of the study are to evaluate the effect of cigar flavours on (1) nicotine exposure, (2) behavioural measures of abuse liability and (3) subjective measures of abuse liability.

METHODS AND ANALYSES

Patient and public involvement

Neither patients nor the public were involved in the formulation of research questions, outcome measures, experimental design, recruitment or conduct of the study. Results from the study, as well as additional information about the study, will be provided to participants on request.

Study design

This study involves 25 current young adult cigarette smokers who complete five Latin square ordered,

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within-subject laboratory conditions that differ by the tobacco product used: (1) own brand cigarette (positive control), (2) original-flavoured B&M cigar, (3) apple-flavoured B&M cigar, (4) cream-flavoured B&M cigar and (5) wine-flavoured B&M cigar. The study takes place in a clinical laboratory setting at Virginia Commonwealth University (VCU). VCU is a diverse, urban campus located in Richmond, Virginia, USA.

Study population

The study population is young adult (18–25 years old) cigarette smokers from the greater Richmond area who report little to no experience with cigars, cigarillos or little cigars (naive; smoked no more than 50 cigar products of any type in lifetime with no more than 10 cigars in the past 30 days) and who are not planning to quit smoking cigarettes in the next 30 days.

Inclusion criteria

To be included, participants must be healthy, as determined by self-report and by measured heart rate/blood pressure (HR/BP), ages 18–25 and willing to provide informed consent. They must agree to attend laboratory sessions and abstain from tobacco/nicotine as required, to use the designated products and to follow the study protocol. Participants are regular cigarette smokers (≥5 cigarettes/day for the past 3 months) naive to cigar products, who provide a semiquantitative urine cotinine result of ≥3 (100–200 ng/mL) at screening (NicAlert test; Jant Pharmacal Corporation, Encino, Los Angeles, California, USA).

Exclusion criteria

Individuals with a self-reported history of chronic diseases or psychiatric conditions are excluded. A chronic disease in this study is defined as any chronic medical condition that an individual has had for 3 or more months. Other exclusion criteria are: history of or active cardiovascular disease, current oral health problems or injuries, low/high BP (self-reported or confirmed during screening), seizures or other medical conditions/allergies that may interact with study conditions. Use of regular prescription medication (other than vitamins or birth control) and past-month use of cocaine, opioids, benzodiazepines and methamphetamine (self-report) are exclusionary. Individuals who report using cannabis or alcohol on >20 of the past 30 days also are excluded. Women who report breastfeeding or test positive for pregnancy (by urinalysis) at screening are excluded.

Withdrawal criteria

If a participant fails to comply with the study protocol prior to or during one session, they are offered the opportunity to repeat the condition once. Failure to comply a second time is ground for withdrawal by the principal investigator (PI). Additionally, participants who experience adverse health effects are considered for withdrawal following consultation with the study's medical monitor. Possible adverse health effects include any side effect, injury, sensitivity reaction or any other illness or condition occurring while a participant is in the study. Participants are also permitted to self-withdraw from the study at any point. If they chose to remove themselves from the study, they will receive no future contact from the study site. All participants who are withdrawn at any point, for any reason, will be replaced until a total of 25 participants have completed the study.

Recruitment and enrolment

Interested individuals identify themselves by responding to institutional review board (IRB)-approved advertisements for cigarette smoking research studies. Participants are recruited via in-person recruitment, websites, message boards, print advertisements, web-based advertisements (eg, craigslist.org) and approved tobacco study registries. Participants begin by completing a survey, either by phone or online, to assess eligibility. Participants also are provided the opportunity to consent to joining a registry, and, should they consent, any answers that are provided are maintained for future contact purposes. If a participant is deemed potentially eligible, they are invited into the laboratory to undergo an in-person screening visit that includes administration of informed consent procedures and assessment of additional eligibility criteria. The study is explained fully to the potential participant, and, after being provided adequate time to read the information and ask questions, participants are asked to sign and date the informed consent document.

Following consent, participant eligibility is confirmed via a baseline questionnaire. Participants are also asked to provide a urine sample, which is used to test for cotinine levels to verify smoking status and, for women, to test for pregnancy. Additional physiological data are collected from participants for eligibility and baseline assessment purposes (ie, height, weight, baseline BP, baseline HR and expired breath CO levels). Following review of all baseline information, eligible participants are then enrolled into the study.

Condition assignment and materials

After enrolment, eligible participants are assigned a condition order and scheduled for the first of five sessions. Participants attend one session for each of the five conditions, each occurring at least 48 hours apart. Condition orders are counterbalanced using a Latin square to help control for carryover effects. The Latin square was created in advance, reviewed by the study statistician for accuracy and is stored in a secure, password-protected database that is only accessible to study staff. The study staff are unblinded to condition orders and prepare the appropriate session product prior to each session. Participants are blind to the flavour assignment for B&M conditions. The own brand cigarette session is not blinded, as the product visibly differs from cigars.

Four flavours of plastic-tipped B&M cigars (John Middleton, Altria; Richmond, Virginia, USA)—stored in a dark, dry, temperate location in order to minimise

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the possibility of staleness or mould—are used: 'Apple', 'Cream', 'Wine' and 'Original'. The fifth condition, own brand cigarette, functions as a positive control. Self-reported own brand cigarettes are purchased locally by the study staff following enrolment and are stored in a separate container in the same location as the cigars.

Compensation

Participants are compensated for their time and inconvenience at the end of each session and study compensation is delivered in increasing amounts across sessions to encourage retention. Participants who complete the entire study are paid $360 in total (session 1=$50; 2=$60; 3=$70; 4=$80; 5=$100). Participants are provided the opportunity to receive up to an additional $10.24 during each session depending on choices made and randomly chosen for reinforcement during completion of the behavioural measures.

Measurement instruments

Baseline questionnaire

The baseline survey is a computer-based self-assessment that includes items regarding demographic characteristics, health history, tobacco use, alcohol use, drug use, tobacco product harm perceptions, nicotine dependence and time preferences. Demographic characteristics include race/ethnicity, age and employment status. Health history includes yes/no items assessing history of or active cardiovascular disease, low/high BP, seizures, depression, anxiety and other physical health/psychiatric conditions as well as regular prescription medication use. Tobacco use items include ever use and past month use of cigarettes, cigars, hookah, smokeless tobacco and electronic cigarettes as well as more detailed measures regarding cigarette smoking behaviour/history and number of cigar products used in lifetime. Tobacco product harm perception items were adapted from standardised national surveys.[42 43] Nicotine dependence was assessed using the Fagerstrom Test for Nicotine Dependence.[44] Four questions that followed a similar format, 'Would you rather win/lose $20 now or $30 a year from now?', were asked to assess time preference.[45]

Biological and physiological measures

Before and after each smoking bout (for a total of four times per session), participants provide saliva samples using methods and procedures consistent with Salimetrics 'Passive Drool with Saliva Collection Aid'.[46] Saliva samples are frozen immediately (−80°C) following collection for later analysis, conducted by a partner laboratory using previously developed assays.[47] Saliva and plasma nicotine levels have been found to be highly correlated in an examination of exposure via the nicotine patch (r=0.82),[48] and saliva nicotine has been used in acute exposure CTC paradigms among adolescents with greater exposure noted among more dependent smokers.[49] Further, saliva assays of nicotine are less invasive and potentially more sensitive than plasma, as saliva nicotine concentrations are higher relative to plasma.[48 50] Secondary physiological measures include expired air CO concentration, as well as HR and BP. Expired air CO is assessed via a BreathCO monitor (Vitalograph, Lenaxa, Kansas, USA). HR/BP is measured and saved electronically using software and equipment that also sounds an alarm if safety parameters are exceeded (Model 506, Criticare Systems).

Behavioural measures

Three behavioural choice tasks (cigarette/cigar purchase task, cross product purchase task and multiple choice procedure) are administered at the completion of each session to assess abuse liability. The cigarette/cigar purchase task (adapted from Jacobs and Bickel[34]) is a hypothetical purchase task wherein participants are asked how many times they would take 10 puffs of the session product (cigar or cigarette depending on condition assignment) if they were offered at each of 16 different prices ($0.00, $0.01, $0,02, $0.04, $0.08, $0.16, $0.32, $0.64, $1.28, $2.56, $3.84, $5.12, $6.40, $7.68, $8.96, $10.24). This measure has been shown to approximate actual consumption of addictive substances.[51] The cigarette and cigar purchase tasks produce five outcome measures: breakpoint, the price at which participants switch from choosing the tobacco product to choosing money; elasticity (price sensitivity), a measure of how hypothetical consumption changes in response to changes in price; intensity, hypothetical consumption at $0 (free); Omax, the maximum hypothetical expenditure across prices (ie, the maximum of the product of reported consumption and price); and Pmax, the price corresponding to Omax. Breakpoint, intensity, Omax and Pmax will be derived directly from the data,[35] while elasticity will be calculated using the following equation from Koffarnus *et al*.[52]:

$$Q = Q_0 \times 10^{k(e^{-\alpha Q_0 C}-1)}$$

In the equation above, Q is consumption at a given price, Q_0 is consumption at $0 (also known as intensity), α is elasticity, C is price and k is a constant representing the span of the data in $\log_{10}$ units. The value of k is typically set equal to the $\log_{10}$ of the highest reported consumption value minus $\log_{10}$ of the lowest reported consumption value, so we will determine the appropriate k value once data are collected, but we will also consider other values of k that provide the best fit for the data as determined by goodness of fit (R^2 values) for demand curves.

Cigarette/cigar purchase task data for each participant will be assessed for usability using two of Stein *et al*.'s three criteria for non-systematic data identification.[53] The two criteria are *trend*, or whether consumption generally decreases as price increases, and *bounce*, or whether there are multiple instances of increases in consumption between consecutive prices and this jump in consumption exceeds 25% of the original consumption at $0. Stein *et al*.'s third criterion, *reversals from zero*—which suggests discarding data when any non-zero consumption is reported after two reports of zero consumption at consecutively increasing prices—will not be used.

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This difference is because our computer-based purchase task ends the task after two consecutive reports of zero consumption, so reversals from zero will not be observed. Data not meeting these criteria will be discarded from cigarette/cigar purchase task analyses.

The cross-product purchase task is a similar hypothetical purchase task that asks participants how many times they would purchase 10 puffs from their own brand cigarette at various prices in the same range as described above when 10 puffs of the session-specific cigar is also available at a constant price ($1.00); this task is administered only during the four cigar conditions. The cross-product purchase task produces cross-price elasticity,[54 55] defined for each participant as the slope from a regression of log-consumption of cigars (at the fixed price of $1) on log-cigarette price. A positive value for this slope would suggest that the flavoured cigar is (at least partially) substitutable for own brand cigarettes.

The multiple choice procedure involves participants making choices between tobacco products and various amounts of money.[38] In the current study, this task shows three columns consisting of 15 different choices: the first column assigns a choice number to each of the choices, the second column provides the option of 10 puffs of the session product and the third offers various amounts of money in amounts that increase as choice number increases ($0.01–$10.24; identical to the cigarette/cigar purchase task except for the lack of $0.00 option). The participant makes 15 different decisions between 10 puffs of the session product and various amounts of money. Once the decisions are made, one of these 15 decisions is selected via a random draw of a ball from an opaque bag; each ball is numbered 1–15 to reflect one of the numbered choices in the task. If the result of the randomly selected choice is 10 puffs of the session product, the participant is given a 10 min consumption period in which to smoke 10 puffs of the session product (ad lib), after which the participant undergoes an additional 10 min rest period prior to the end of the session. If the randomly selected choice is one of the amounts of money, the participant is given that amount of money immediately, followed by a 10 min 'consumption' period and a 10 min rest period. The multiple choice procedure produces the crossover point, measured in US dollars, which represents the highest price at which participants chose the tobacco product instead of the money.[39 56 57] Data will be excluded for those participants with inconsistent choices (ie, those who switch back from choosing money to choosing tobacco products at higher prices).

A secondary behavioural measure of smoking behaviour (puff topography) is collected during the two smoking bouts (10 directed puffs per bout, 30 s interpuff interval) per session using the eTop topography instrument developed and manufactured at the American University of Beirut (AUB). The AUB research group has a record of topography instrumentation development for alternative tobacco products.[58] Similar to commercially available cigarette topography instruments, the instrument senses flow-induced pressure drop across an orifice incorporated into the mouthpiece. The pressure drop is sensed by a pressure transducer whose output voltage every 100 milliseconds is amplified, digitised and sampled. Specific topography measures of interest include puff duration, average puff volume, flow rate and total puff volume inhaled. Mouth pieces for cigars and cigarettes are individually calibrated prior to each session to relate puff velocity (mL/s) to the pressure transducer voltage signal.[59 60]

Subjective measures

Subjective measures are assessed at nine points during each session. Subjective measures consist of the short-form of the Addiction Research Centre Inventory consisting of 49 true–false items,[61] the general Labelled Magnitude Scale for rating flavour intensity,[62] the Direct Effect Scale[63] and the Direct Effects of Tobacco Scale.[64 65] An additional 12 items are designed to assess tobacco abstinence symptoms and more general drug effects and include items like 'Urges to smoke a cigarette' and 'Do you feel a rush?'. Each of these measures has been used previously to assess the subjective effects of a variety of drugs and tobacco products.[66–68]

Primary outcomes

The primary outcomes of this study include physiological, behavioural and subjective measures. The primary physiological outcome is saliva nicotine. Primary outcomes for behavioural measures of abuse liability are breakpoint, elasticity, intensity, Omax and Pmax from the cigarette/cigar purchase task, cross-price elasticity from the cross-product purchase task and crossover point from the multiple choice procedure. Subjective measures predictive of abuse liability, reinforcing effects and acceptability-related items are used as the primary subjective outcomes.

Secondary outcomes

The secondary outcome measure is puff topography, a behavioural measure of smoke inhalation that can be indicative of toxicant exposure.[69] Puff topography data will be collected during both bouts in each session and includes puff duration, average puff volume, flow rate and total puff volume inhaled.

Session timeline

Prior to each session, participants are instructed to abstain from nicotine/tobacco for at least 12 hours. Abstinence is verified by measuring expired air CO levels at the beginning of each session. Participants with an expired air CO reading >10 ppm are considered non-compliant with abstinence requirements, rescheduled if applicable and provided an opportunity to comply with session protocol on another day. Once compliance with the abstinence period is verified, physiological data collection will begin and participants are instructed to rinse their mouth with water to remove any food residue and begin a 30 min rest period in order to achieve resting HR and BP (figure 1). Following the rest period, participants provide

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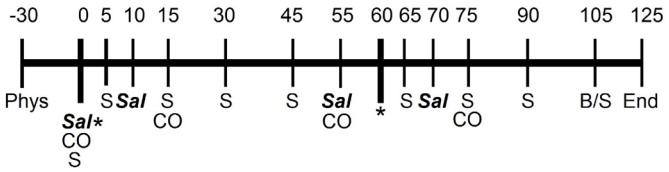

Figure 1 Session timeline in minutes. *, 10 puffs of session product administered; B, behavioural measures administered; CO, expired air CO measured; End, physiological monitoring ends; Phys, physiological monitoring begins and mouth rinse; S, subjective measures administered; Sal, saliva collection.

a saliva sample, expired air CO is measured and subjective measures are completed.

Product administration begins following completion of baseline subjective measures. Product administration consists of 10 directed puffs with a 30 s interpuff interval and is monitored and recorded using a puff topography system. There are two product administrations during each session, with the second occurring 60 min after the first. The participant completes subjective measures at 5, 15, 30 and 45 min following each product administration (including baseline, nine times in total). Saliva is collected 10 min after each product administration and 5 min before the second product administration (four saliva samples per session). To assess CO boost, expired air CO concentration is assessed at baseline, 15 min after each product administration and 5 min before the second product administration (four CO assessments each session). HR/BP are recorded throughout the entire session. Following both product administrations and completion of all subjective measures, behavioural task measures are assessed by completion of either one or two hypothetical purchase tasks (cigarette purchase task during the own brand cigarette condition; cigar purchase task and cross-product purchase task during cigar conditions) as well as the multiple choice procedure for cigarettes in the own brand condition and for the session-specific cigar in the cigar conditions.

Data monitoring, sample requirements and statistical analyses

Data and safety monitoring

All baseline questionnaire and subjective response data are collected at the study site and entered electronically through the Research Electronic Data Capture system (REDCap[70]), a secure database system, hosted at VCU, and resemble paper forms that received the approval of the study site IRB. Data quality of participant-entered forms are monitored by site personnel during all sessions for completeness, validity and integrity. In the cases where study personnel observe incomplete or inconsistent responses, study personnel verify responses with participants and update the electronic record if needed. Data entered by personnel are checked for accuracy by other site personnel and detailed item inquiries are recorded and tracked. Review and modifications are made as needed, and any information regarding such modifications are recorded and associated with a study staff member based on REDCap user name. Ability to make such modifications is restricted based on an individual personnel's position and privileges. A response to each inquiry is needed for the queried item to be considered closed. Data will be monitored for quality purposes every 6 months by the PI and coinvestigator.

While adverse events (AEs; ie, incidents of high BP) and serious AEs (SAEs; ie, any AE that requires hospitalisation) are not expected, as this protocol is considered low risk, all research staff who interact with participants are instructed on procedures involved in managing and reporting any potential AEs and SAEs. Any AEs or SAEs are well documented, and these records will be maintained for regular review by the study staff. AEs and SAEs are monitored during sessions by study staff and assessed by the researcher for severity and expectedness/relatedness to the study. All documented AEs are reviewed by the PI and coinvestigator within 1 week of occurrence; SAE documentation is reviewed within 24 hours. Further, in the case of an SAE, the medical monitor also is notified and consulted. All AEs are reported to the study site IRB as part of an annual report, while all SAEs that are unexpected and deemed related or possibly related are reported to the study site IRB within two business days and to the study sponsor within 72 hours.

Sample size

This study will recruit 25 young adults 18–25 years of age. This number was necessary to detect moderate within-subjects effects (ie, f=0.35) with power >0.80 between conditions for the primary outcome measures, assuming a moderate correlation between measures (r>0.50).

Quantitative analyses

Following data cleaning and preparation, linear mixed-effect models including two within-subject factors (condition and time) will be used to assess the condition effect on the physiological (saliva nicotine), behavioural (cross-over point, breakpoint, elasticity, intensity, Omax, Pmax and cross-price elasticity) and subjective effect outcomes. Mixed-effect logistic or linear models will be fit to the data depending on the distribution of the error term. All models use an independent covariance matrix and estimate robust standard errors. Predicted probabilities (logistic mixed-effects models) and predicted values (linear mixed models) for condition effects will be estimated with bootstrapped CI. We will also test for jointly significant condition effects across models of physiological, behavioural choice task and subjective measures of abuse liability. Secondary outcomes (CO, HR, BP, average puff volume, puff duration, flow rate and total puff volume) will be analysed similarly. All analyses will be performed in Stata V.15.

ETHICAL CONSIDERATIONS AND DISSEMINATION

Ethics approval was granted. All personnel were trained on study procedures, conducting research with human

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subjects and data safety and monitoring protocols. This study was funded by the National Institute on Drug Abuse of the National Institutes of Health and the Food and Drug Administration (1R03DA043005) and was registered at ClinicalTrials.gov with protocol number NCT0237051.

Dissemination channels for study findings will include publishing in the scientific literature, presentations at scientific meetings and a policy brief to communicate the implications of the study's findings to policymakers and communities.

STUDY STATUS

Study recruitment began in March 2017. The target sample size is n=25. As of the time of this submission (April 2018), 30 participants have been consented, 12 failed in-person eligibility screening, three have withdrawn, one is currently enrolled and 14 have completed the study. Recruitment is expected to be completed by May 2018.

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