Title: The Effect of Electronic Cigarette Liquid Characteristics in Smokers.

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Background, Rationale and Goals

1. * Describe the study's background and what is currently known from the scientific literature, including citations, or upload a citation list in document upload. Use lay language whenever possible.

Electronic cigarettes (ECIGs) use a battery-powered heating element to vaporize a liquid that usually contains nicotine; the user inhales the resulting aerosol. ECIG popularity is increasing in the US and the fact that 23.1% of ECIG users report frequent, daily use (Coleman et al., 2017) suggests that these products may have tobacco cigarette-like "abuse liability". That is, as with tobacco cigarettes, ECIGs may have a similar likelihood of maintaining persistent use and dependence. ECIG abuse liability could be influenced by factors that affect nicotine delivery, such as device power, liquid nicotine concentration, and user puffing behavior such as puff number and duration (i.e., puff topography). Another factor that might influence ECIG abuse liability is flavor, and there are over 7,000 ECIG liquid flavors available on the US market (Zhu et al., 2014). While some of these flavors are related to tobacco cigarettes (e.g., tobacco, menthol), many are not, and instead fall into categories related to fruit (e.g., berry), candy (e.g., gummy bear), or dessert (e.g., ice cream). A common theme among these categories is that they represent sweet foods, and, in fact, sweeteners such as ethyl maltol and sucralose are common ECIG liquid ingredients (Fagan et al., 2017; Rao et al., 2017; Rosbrook et al., 2017). Perceived sweetness increases ECIG appeal and thus may enhance ECIG abuse liability (Goldenson et al., 2016; Rao et al., 2017).
Enhanced ECIG abuse liability may have negative outcomes, in that it may contribute to non-tobacco users becoming nicotine-dependent ECIG users, but may also have positive outcomes, in that it may facilitate current tobacco cigarette smokers becoming former smokers. Unfortunately, few studies have examined the abuse liability of ECIGs, and none have manipulated the sweetness of ECIG liquids.

Abuse liability assessments are often conducted in clinical labs that offer powerful within-subject designs and rigorous control of experimental conditions (e.g., device power and liquid nicotine concentration). Common abuse liability measures include behavioral tasks that assess how much participants value a drug in terms of money (e.g., purchase task) or work (e.g., progressive-ratio task or "PRT"). For example, for tobacco products, the PRT has been used to assess the extent to which participants will perform increasing amounts of work (e.g., press a button) to self-administer a product (e.g., take a puff; Audrain-McGovern et al., 2016; Barrett, 2010; Stein et al., 2017). The PRT's primary outcome measure is the "breakpoint": the maximum work/effort individuals are willing to expend to self-administer a drug. The PRT has been used to assess the abuse liability of a variety of drugs (Babalonis et al., 2013; Bolin et al., 2013; Stoops, 2009), including comparisons across nicotine-containing products (Barrett, 2010; Stein et al., 2017). When combined with other measures related to abuse liability, such as plasma nicotine concentrations (nicotine delivery), subjective effects, and puff topography, the PRT allows for a more comprehensive assessment of product abuse liability. Studies investigating ECIG abuse liability are limited, and there are currently no studies examining the abuse liability of sucralose. The proposed studies will use clinical lab methods to examine the impact of sucralose on ECIG abuse liability. Results will provide insight on factors influencing ECIG user dependence and health risks that can inform upcoming electronic cigarette regulations.

References
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2. * **Describe the study hypothesis and/or research questions. Use lay language whenever possible.**
The purpose of this study is to determine the influence of a common added ECIG liquid sweetener, sucralose, and nicotine on electronic cigarette abuse liability. This study aims to examine differences in willingness to 'work' for the product (progressive ratio task), willingness to hypothetically pay for the product (purchase task), nicotine delivery, use behavior (puff topography), subjective effects, and physiological effects when cigarette smokers use an electronic cigarette with and without sucralose and nicotine compared to participants' own brand of cigarettes.

We hypothesize that participants will perform more work for puffs when using the sweetened electronic cigarette liquid with nicotine, relative to other electronic cigarette conditions, though we predict that participants will work the hardest for their own brand of cigarettes. In addition, we hypothesize that the sweetened electronic cigarette with nicotine will have greater nicotine delivery than the other electronic cigarettes, but lower relative to participants' own brand of cigarettes.

3. * **Describe the study's specific aims or goals. Use lay language whenever possible.**
The aims of this study are to better understand how electronic cigarette liquids with and without added sweeteners (sucralose) and nicotine effect the abuse liability of electronic cigarettes, and compare that to the abuse liability of traditional cigarettes. Abuse liability will examined using a lever pressing work task (i.e., Progressive Ratio Task), a hypothetical willingness to pay task (i.e., Cigarette Purchase Task), nicotine delivery, and subjective effects.

4. * **Describe the scientific benefit or importance of the knowledge to be gained:**

The benefits of this research are of a scientific nature, which should in the long-term benefit society at large. In particular, the use of ECIGs has become increasingly popular. There is a lack of information about ECIGs and their effects. The results of this study will inform future work regarding the abuse liability of ECIGs compared to cigarettes in cigarette smokers.

5. * **Describe any potential for direct benefits to participants in this study:**
None.

6. * **Describe any potential for direct social impact in this study . For example, any engagement with specific communities to respond to community-identified needs, or ways the study will strengthen the well-being of the specific communities if applicable:**
This study will help inform FDA regulations that aim to uphold the public health standard in regards to the abuse potential of electronic cigarettes and their utility as a smoking cessation aid, with the goal of protecting public health.

Study Population

1. * **Provide the maximum number of individuals that**

   1. May participate in any study interaction or intervention (Including screening, consenting, and study activities)
   AND/OR
   2. You obtain any data/specimens about (regardless of identifiability)

   at VCU and at other sites under the VCU IRB's oversight. See the help text for additional guidance.
   300

2. **If this is a multi-Center Project, what is the maximum anticipated number of subjects across all sites?**

3. * **Provide justification for the sample size by explaining how you arrived at the expected number of participants and why this number is adequate for answering the research questions:**
   Thirty participants will be needed to obtain power of at least 0.80 (i.e., 80% chance of detecting an effect) for a difference between conditions on the PRT. The power analysis was based on previous tobacco studies (Ns = 20-24 participants) where effect sizes for the main effect of condition was medium to large for PRT outcomes (f > 0.68), medium to large for plasma nicotine (f > 0.68), and medium to large for subjective items “pleasant”/“craving a cigarette” (f >0.69). The outcome measure with the smallest expected effect size was used to calculate the number of participants needed using condition means from previous clinical studies of tobacco products assuming a small or a moderate correlation between repeated measures (Barcikowski & Robey, 1985).

4. * **List the study inclusion criteria:**
   Individuals must be healthy (determined by self-report), 21-55 years old, willing to provide informed consent, attend the lab sessions, and abstain from tobacco/nicotine as required. All participants must use ≥ 8 cigarettes per day and have not used an ECIG in the past 30 days. Cigarette smokers must have a CO level at screening of at least 10 ppm (as in Hiler et al., 2017) and report trying an electronic cigarette at least once in their lifetime.

5. * **List the study exclusion criteria:**
   Individuals with the following self-reported current, diagnosed medical condition(s) will be excluded automatically: heart-related conditions (e.g., recent heart attack/stroke, coronary heart disease), severe immune system disorders (e.g., HIV/AIDS, multiple sclerosis), respiratory disorders (e.g., COPD, asthma), kidney diseases, liver diseases (e.g., cirrhosis), or seizures.

   Individuals with other self-reported current, diagnosed medical conditions (e.g., diabetes, thyroid disease, lyme disease) will be considered for exclusion after consultation with the PI and medical monitor. Participants with any medical condition/medication that may affect participant safety, study outcomes, or biomarker data will be excluded based on these consultations.
   Participants who are under the care of a doctor for a diagnosed psychiatric conditions or who report current psychiatric treatment or psychotropic medication use will be excluded.

   Individuals with past month use of cocaine, opioids, benzodiazepines, and methamphetamine will be exclude. Individuals who report using cannabis greater than 15 days in the past 30 and/or alcohol greater than 25 days in the past 30 days will be excluded. Participants who choose not to answer question related to inclusion/exclusion criteria will be excluded. Women will be excluded if they are breast-feeding or test positive for pregnancy (by urinalysis) at screening. Participants who weigh less than 110 pounds will also be excluded. Individuals will also be excluded if they self-report past 30-day use of ECIGs, to avoid recruiting dual-use populations that may be less able to abstain from nicotine-containing products prior to lab sessions. We are excluding individuals who indicate that they intend on quitting smoking in the next 30 days and instead referring to cessation treatment.

6. * **Will individuals with limited English proficiency be included in or excluded from this research?**

- ○ Included
- ◉ **Excluded - safety concerns if participants are unable to communicate with the study team**
- ○ Excluded - instruments/measures only validated in English
- ○ Excluded - no prospect of direct benefit to individual participants
- ○ Excluded - minimal risk study
- ○ Excluded - lack of budget/resources for translation and interpretation [provide an explanation in next question]
- ○ Excluded - other reason [provide an explanation in next question]

7. **Justify the inclusion and exclusion criteria if you are either targeting, or excluding, a particular segment of the population / community. Provide a description of the group/organization/community and provide a rationale.**
We are not targeting nor excluding any particular segment of the population based on demographic criteria.

We are targeting cigarette smokers ages 21-55 years old for their participation in this study. We are excluding individuals who are 18-21 based on Virginia's new tobacco purchase laws. Furthermore, electronic cigarettes are often marketed towards cigarette smokers as cigarette alternatives, therefore, recruiting cigarettes smokers for this study increases the validity of the results of the study. Lastly, cigarette smokers who smoke at least 8 cigarettes a day will be less likely to experience negative side effects from using nicotine containing products, like the electronic cigarettes used in the current study. We are excluding individuals who intend on quitting in the next 30 days to avoid giving participants nicotine products who may otherwise would not intend on on using nicotine products.

Study Procedures

1. * **Describe the study hypothesis and/or research questions. Use lay language whenever possible.**
The purpose of this study is to determine the influence of a common added ECIG liquid sweetener, sucralose, and nicotine on electronic cigarette abuse liability. This study aims to examine differences in willingness to 'work' for the product (progressive ratio task), willingness to hypothetically pay for the product (purchase task), nicotine delivery, use behavior (puff topography), subjective effects, and physiological effects when cigarette smokers use an electronic cigarette with and without sucralose and nicotine compared to participants' own brand of cigarettes.

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2. * **Describe the study's specific aims or goals. Use lay language whenever possible.**
The aims of this study are to better understand how electronic cigarette liquids with and without added sweeteners (sucralose) and nicotine effect the abuse liability of electronic cigarettes, and compare that to the abuse liability of traditional cigarettes. Abuse liability will examined using a lever pressing work task (i.e., Progressive Ratio Task), a hypothetical willingness to pay task (i.e., Cigarette Purchase Task), nicotine delivery, and subjective effects.

3. * **Choose all types of recruitment materials that may be used and upload them below:**

   - ☑ **E-mail invitations**
   - ☑ **Phone Solicitation scripts (i.e. cold calls or random-digit-dialing)**

- [x] **Flyers, Mailed Letters or Newspaper/TV/Radio Ads**
- [x] **TelegRAM announcements**
- [x] **Website text**
- [ ] Study-specific web sites (provide the design and text)
- [x] **Social Media**
- [ ] EPIC MyChart Patient Portal research study descriptions
- [ ] Psychology Research Participant Pool (SONA) study descriptions
- [ ] Scripts for announcements made to groups
- [ ] Other recruitment document
- [ ] No recruitment materials

4. * **Describe the study procedures/methods for identifying and recruiting participants. Address all of the following three aspects of recruitment in your response.**

1. Identification of potentially eligible participants or secondary data/specimens of interest.
- What database(s) will be queried to identify secondary data/specimens
- How VCU Informatics or VCU IRDS will be used for cohort identification (when applicable, see help text)
- How potential participants' contact information will be obtained

2. Recruitment procedures to invite participation in the study (when applicable):
- How each of the written or verbal recruitment materials and reminders (selected above) will be used
- Who will contact, approach, or respond to potential participants
- Locations where recruitment procedures will take place
- The timing and frequency of recruitment attempts

3. Eligibility screening prior to consent and how those activities will be carried out (when applicable)

See the help text for additional guidance.
Participants will be recruited via word-of-mouth and advertisements that will be posted as flyers around the community, in newspapers, on Craigslist, in TelegRAM and on social media sites such as Facebook and/or Twitter. Any postings on internet sites will use exactly the same information that is presented in those previously approved flyers (we will use advertisements that are already approved as part of the CSTP registry: HM20002567). Potential participants will make the initial contact via telephone by calling the phone number provided on the advertisements, or by going to the website provided on the advertisements. Please note that for the initial screening, we will use a multi-study screening process/registry described in HM20002567. Participants who appear eligible based on the initial screening questionnaire (in HM20002567 and attached) are then contacted (either via phone or e-mail), told about this study using only language from the approved consent form (via phone), and if interested, participants are invited for an in-person screening, where consent for this study will be obtained.

If potentially eligible, HM20002567/HM20015258 staff will use administrative features (i.e., administrative fields/forms) in REDCap to create an internal report that is used to contact/follow-up potentially eligible and enrolled participants for the current protocol using their registry ID. No data will be directly transferred to the current protocol to or from either registry. Use of administrative fields and study staff that are aware of their responsibilities on related protocols eliminates the need for this additional activity.

At the in-person informed consent/screening appointment, participants will first complete informed consent procedures. After agreeing to be in the study, participants are assigned a unique numeric code (study ID) specific to this protocol. This study ID is used to identify all subsequent study-related information/data. Following enrollment, the study ID is added to the participant's registry record/ID (HM20002567) in an administrative form thus electronically linking the registry ID (where contact information is housed) to their study ID (HM20015258). This technique is used so we can communicate effectively with participants as well

as reduce the number of places/REDCap projects where participant contact information is stored. The study ID field (HM20015258) is deleted from the registry project (HM20002567) when recruitment for the study has been completed.

Individuals who are participants in other, ongoing CBPL studies (participants with whom we have a pre-existing relationship) may be verbally referred to this study, and directed to either call the laboratory or visit the website indicated on the advertisements/flyers, if they are interested.

Participants who are eligible and who choose to enroll may be contacted via text for appointment reminders if they agree (see scripts).

5. * **Does this study have a separate protocol document (i.e. a multisite or sponsor's protocol) that contains a detailed description of the study's methodology?**

- ○ Yes
- ◉ **No**

6. * **Since a separate protocol document is not uploaded, describe the proposed research using language understandable to those IRB committee members whose expertise is not scientific. The description must include:**

1. A statement explaining the study design
2. A detailed description of all the procedures that will be followed to carry out the study, preferably in sequential order, and in sufficient detail that the study's methods could be replicated
3. The schedule and frequency of when and how procedures will be conducted (e.g. in person, online, phone, paper, etc.)
4. A description of all research measures/tests/interventions that will be used, including analyses/tests conducted on specimens/biological samples (if applicable)

See the help text for additional guidance
Screening process:
Interested potential participants will make initial contact. Participants will first be screened via phone or online, via a multi-study screening process/registry described in HM20002567, which is approved and which has its own associated consent form (see attachment "CSTP Studies Screening and Registry"). Participants can tell study staff if they are interested in screening for a particular study only.

Consent and in-person screening:
Participants who appear eligible during the initial phone or online screen will then be scheduled for an in-person screening visit. Participants will be provided a hard copy of the consent form and will be presented with a voice-over PowerPoint presentation explaining the consent form. After having their questions answered, participants who choose to participate in the study and provide informed consent will complete other forms (see in-person screening forms: ICF, Health Information Form, Biochemical test/vitals form, Fagerstrom Test for Nicotine Dependence, Demographic form). These will be completed on paper forms or via RedCap. Age will be verified by asking participants to provide some form of identification that includes a date of birth. If participants are very clearly over age 30, we may not check ID. Participants will provide an expired breath CO sample to confirm regular cigarette use (CO > 10 ppm). Women will have their urine tested for pregnancy. Also during this time, participants will be able to view other questionnaires (Hughes-Hatsukami Questionnaire (HH), Tiffany-Drobes Questionnaire of Smoking Urges (QSU), a modified version of the Cigarette Evaluation Questionnaire (CEQ), Positive and Negative Affect Schedule (PANAS), Drug Effects Questionnaire (DEQ), Direct Effect of Nicotine scale (DEN), the General Labeled Magnitude Scale (GLMS), Labeled Hedonic Scale (LHS), and willingness to use product again questionnaire (WUA), via computer, and the study equipment. This initial in-person screening will be separate from the first experimental session. After screening and informed consent, eligible participants will enroll in the study. A total of 30 participants are needed to complete this study.

Study sessions:
Once enrolled, participants will attend the lab for five ~3.5 hour additional experimental sessions where they

use a 30 Watt ECIG set to either 0.5 Ohms, which will contain either 0 mg or 15 mg nicotine-containing unflavored liquid that is either sweetened or unsweetened with sucralose or their own brand of cigarettes. The study conditions will be Latin-square ordered. The sessions will occur no more than 2 days per week and will be separated by at least 48 hours. The approximate total time that participants will be in the laboratory is 18.5 hours (1 hour for screening and 17.5 hours for sessions). This does not include the 12 hours before each session that we ask participants to abstain from nicotine/tobacco use.

Sessions will be preceded by 12 hours tobacco/nicotine abstinence (to measure the extent to which each product suppresses nicotine/tobacco abstinence symptoms). Participants will verify abstinence from combustible tobacco (e.g., cigarettes) by taking a CO breath test prior to each session (participants must have an exhaled CO reading of ≤10 ppm or 50% of their screening CO concentration in order to participate). Participants will be asked questions about symptoms experienced since the last visit. To ensure at least 1-hour abstinence prior to the study onset, participants will undergo a 1-hour acclimation period whereby they can read, watch movies, or pass the time however they please in the study session room. This 1-hour acclimation period ensures participants are at least 1-hour abstinent from nicotine and tobacco products as has been done in previous (HM20004850; HM20012671) study protocols. Collectively, participant compliance with abstinence requirements is important and the methods proposed here have been effective in past and ongoing protocols.

Once participants are deemed abstinent and complete the 1-hour acclimation period physiological monitoring equipment will be attached (pulse oximotor placed on finger). After a participant's blood pressure is determined to be within a safe range for participation, the arm cuff will be removed. A detailed timeline of the sessions is described below. Please note that because blood draws can be difficult, we will attempt to sample blood no more than three times in one day, and if all three attempts are unsuccessful, the session will be discontinued, with payment as outlined in the consent and compensation section. A baseline blood sample will be taken and baseline subjective questionnaires will be administered. Following baseline assessments, participants will complete a 10-puff directed bout in which puffing topography is recorded (see below for additional details about recording puff topography) immediately followed by a second blood sample and a second set of subjective questionnaires. Participants will then be asked to complete the Cigarette Purchase Task (CPT) and the cross-product CPT (or a modified version for the ECIG conditions). A third set of subjective questionnaires will be administered and then participants will then be asked to complete a 30-minute progressive ratio task (PRT), in which participants can chose to work for product puffs by button pressing on a computer. Following the completion of the PRT, participants will be asked to complete a final set of subjective questionnaires administered. All subjective questionnaires will be administered via computer or RedCap. Participants will have another 30 minute wait period after the completion of the PRT and then they will be compensated for their time.

The CBPL contains four mouthpiece-based, puff topography recording instruments that require that the electronic cigarette or cigarette be placed in a specialized mouthpiece that can detect flow-induced pressure changes across an orifice in the mouthpiece as a result of an inhalation. The pressure changes are sensed by a pressure transducer and converted to flow rate (puff velocity) via previously calibrated software. The converted flow rate measurements are subsequently used by the software to calculate other puff topography variables such as puff duration, volume, number, and interpuff-interval (Blank et al., 2009). Importantly, the device provides sensitivity sufficient to ensure valid measurements at puff velocities as low as 3 ml/sec because topography devices used to study tobacco cigarette smoking behavior may not be sensitive enough to measure accurately the low flow rates (i.e., puff velocities) observed with ECIG use (Spindle et al., 2014).

Experimental session timeline (times approximate):

-00 Hr 00: Participant arrives, complete pre-session symptom checklist, 1-hr acclimation period begins (CO test).

-1 Hr 00: Attach physiological equipment.

-1 Hr 10: Baseline blood sample, baseline subjective effects questionnaires
Subjective questionnaires: HH, QSU, DEN, PANAS

-1 Hr 15: 10 puffs from ECIG/cigarette (30s inter-puff interval)

-1 Hr 20: Blood sample (immediately after last puff), subjective effects questionnaires
Subjective questionnaires: HH, QSU, PANAS, DEN, GLMS, LHS, DEQ, CEQ, WUA

-1 Hr 45: Cigarette Purchase Task (CPT) and Cross Product CPT

-2 Hr 20: Subjective effects questionnaires: HH, QSU, PANAS

-2 Hr 30: Progressive Ratio Task

-3 Hr 00: Subjective effects questionnaires: HH, QSU, PANAS

-3 Hr 30: Participants disconnected from physiological equipment, compensated, and released

7. * **The IRB only reviews research activities, so indicate for each of the study activities described in the question above or in the protocol which activities are:**

- Being performed exclusively for research purposes (i.e. they would not otherwise be done apart from this study) VERSUS.
- Alterations of routine activities/procedures (e.g. the study is altering the timing, frequency, method, location, amount, etc.) VERSUS.
- Being done for other purposes and whose data/results will be used secondarily in the study (e.g. standard medical or psychological tests, routine education practices, quality improvement initiatives, etc.).
See the help text for additional guidance

All the study procedures are preformed exclusively for research purposes.

8. **If applicable, describe alternatives (research or non-research) that are available to potential participants if they choose not to participate in this study:**
There is no alternative to this research study besides not to participate in the study.