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Tobacco
Research Center

UCSF

Evaluating the Comparative Pharmacokinetics of Nicotine after administration via JUUL or Tobacco Cigarettes

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1 Contents

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STUDY SITES

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BACKGROUND & PROJECT SUMMARY

Electronic cigarettes (e-cigarettes) have a potential role in smoking cessation and harm reduction for tobacco cigarette smokers. As of 2019, the most popular e-cigarette is JUUL, a pod type device containing e-liquids with high nicotine content. The goal of this study is to better understand the pharmacokinetic and pharmacodynamics responses produced by the JUUL e-cigarette, compared to tobacco cigarettes, in e-cigarette and tobacco cigarette smokers.

2 RESEARCH AIMS

2.1 SPECIFIC AIM #1

To categorize the nicotine PK profile (maximum plasma concentration; time to maximum plasma concentration and area under the concentration-time curve) and compare when using the JUUL e-cigarette vs. a tobacco cigarette in a standardized manner.

2.2 SPECIFIC AIM #2

To categorize the nicotine PK profile (maximum plasma concentration; time to maximum plasma concentration and area under the concentration-time curve) and compare when using the JUUL e-cigarette vs a tobacco cigarette when using the product ad libitum.

2.3 SPECIFIC AIM #3

To evaluate various outcomes following JUUL e-cigarette or tobacco cigarette use, both with standardized and ad lib use including: heart rate, plasma catecholamines, pulmonary function testing.

2.4 SPECIFIC AIM #4

To evaluate and compare the effects on craving, reward and satisfaction when using the JUUL e-cigarette vs. tobacco cigarette.

3 STUDY DESIGN

3.1 DESIGN SUMMARY

This is an observational, crossover design that will examine the pharmacokinetics and pharmacodynamics of impact of smoking tobacco cigarettes or vaping the JUUL electronic cigarette. Participants will recruited in two groups: primary e-cigarette vapers and primary cigarette smokers. The order of assignment to either tobacco cigarettes or the JUUL electronic cigarette will be counter-balanced via a latin square design.

3.2 ENROLLMENT TARGET

We will enroll a total of 30 participants, across two groups; 15 primary cigarette smokers who may have occasionally used electronic cigarettes and 15 experienced electronic cigarette users who occasionally smoke tobacco cigarettes. We will seek to enroll equal numbers in each group, but will remain flexible during recruitment.

3.3 STUDY TIMELINE

1. Preparation for this study began in May 2019
2. Application submitted to the UCSF IRB: July 2019

3. UCSF IRB Initial Approval date: September, 2019
4. Estimated start date: September 2019
5. Estimated end date: September 2023

3.4 ELIGIBILITY

All individuals interested in participating and who meet the inclusion/exclusion criteria will be invited to be part of the study. Inclusion criteria are described below.

3.4.1 Inclusion Criteria

- Healthy on the basis of medical history and limited physical examination, as described below:
    - Heart rate < 105 BPM*
    - Systolic Blood Pressure < 160 and > 90*
    - Diastolic Blood Pressure < 100 and > 50*

  *C*onsidered out of range if both machine and manual readings are above/below these thresholds.*
- Age: ≥ 21 & ≤ 70 years old
- Body Mass Index ≤ 38.0 (*at PI's discretion for higher BMI if no other concurrent health issues*)
- Willingness to avoid combusted marijuana up to 48 hours before each study visit
- Willingness to the avoid use of any non-legally sourced cannabis product for the duration of the study
- Nicotine strength of e-liquid of usual e-cigarette > 0 mg/ml
- ***Group 1 Experienced E-cigarette users***
    - Current use of tobacco cigarettes (<5 cigarettes per day)
    - Current e-cigarette use at least 15 days out of the past 30 days of a non-mod e-cigarette
- ***Group 2 Primary Tobacco cigarette users:***
    - Currently smoking ≥ 5 cigarettes per day
    - Current e-cigarette use must be < 5 times per month
- Saliva cotinine ≥50 ng/ml or urine cotinine and/or NicAlert=6
- Must have a smart phone, computer, or tablet and internet access (for remote procedures)

3.4.2 Exclusion Criteria

- Medical
    - Heart disease
    - Seizures
    - Cancer

  - Thyroid disease (okay if controlled with medication)
  - Diabetes
  - Hepatitis B or C or Liver disease
  - Glaucoma
  - Kidney disease or urinary retention
  - History of stroke
  - An ulcer in the past year
  - Active use of an inhaler for Asthma or COPD
- Psychiatric conditions
  - Current or past schizophrenia, and/or current or past bipolar disorder
  - Major depression, current or within the past year
  - Major personality disorder
  - Participants with current or past minor or moderate depression and/or anxiety disorders will be reviewed by the PI and/or medical monitor and considered for inclusion
  - History of psychiatric hospitalizations are not exclusionary, but study participation will be determined as per PI's or medical monitor's approval
- Drug/Alcohol Dependence
  - Alcohol or illicit drug dependence within the past 12 months (currently in treatment) with the exception of those who have recently completed an alcohol/drug treatment program
  - Positive toxicology test for illicit drugs at the screening visit (THC & prescribed medications okay)
  - Opioid replacement therapy (including methadone, buprenorphine, or other)
- Psychiatric medications
  - Current regular use of any psychiatric medications is exclusionary, with the exception of SSRIs and SNRIs and current evaluation by the PI and/or medical monitor that the participant is otherwise healthy, stable, and able to participate
- Medications
  - Use of sympatholytic medications for cardiovascular conditions including hypertension (Example: beta and alpha-blockers)
  - Use of medications that are inducers of nicotine metabolizing enzyme CYP2A6 (Example: rifampicin, carbamazepine, phenobarbital, and other anticonvulsant drugs)
  - Concurrent use of nicotine-containing medications

    - Any stimulant medications (example: Adderall) generally given for ADHD treatment
- Use of Other Tobacco Products (OTP)
    - Any of the following products in combination more than 15 times in the past month
    - smokeless tobacco (snus, oral snuff, chewing tobacco)
    - pipes
    - cigars, cigarillos, little cigars
    - blunts, spliffs
    - hookah
- Other/Misc. Chronic Health Conditions
- Fainting (within the last 30 days)
- Other "life threatening illnesses" as per PI's or medical monitor's discretion
- Pregnancy
    - Pregnancy (self-reported and urine pregnancy test)
    - Breastfeeding (determined by self-report)
- Concurrent participation in another clinical trial (at PI's discretion)
- Inability to read and write in English
- Planning to quit smoking or vaping within the next 60 days
- Recent onset or change (worsening) in cough, fever and/or abdominal symptoms (vomiting or pain) in the past two weeks
- Diagnosis of pneumonia in the past 3 months
- Uncomfortable with blood draws
- Known allergy to propylene glycol or vegetable glycerin

3.4.3 Eligibility Determination

Eligibility will begin to be determined via a preliminary REDCap online survey. At that time, the CRC will begin an eligibility checklist. The online survey will be followed-up by a phone screen to clarify eligibility questions and the eligibility checklist will be updated. Final eligibility criteria will be evaluated via assessments at the in person screening visit, and saliva cotinine. If the participant is not taking any medications and has no active psychiatric symptoms, the CRC can sign off on the eligibility checklist. Otherwise, the PI and/or Medical Monitor are required to review the participant's chart and sign off on eligibility.

3.4.4 Reassessment of Eligibility

If there is a positive illicit drug tox at screening, participants will be given 2-weeks to come back and re-screen. In that case, all screening visit procedures are repeated.

Additionally, if their 5B Day 1 visit is set to occur 30-90 days past the date of their screening visit, participants will be asked over the phone by the CRC if they had any recent changes in medications, medical care or tobacco/nicotine use to confirm continued eligibility. If the participant's 5B admissions are more than 90 days past the screening visit, the participant will have to be re-screened.

4 STUDY VISITS & WINDOWS

The chart below describes assessment time points and the desired window between visits. The window will remain flexible to accommodate participants' schedules, and to the discretion of the PI if it is deviated from.

Assessment Time Points	Desired Window
REDCap survey	N/A
Phone Screen	N/A
Screening Visit	Within 30 days of Redcap survey
Orientation	Within 90 days of Screening Visit
5B Hospital Study Day 1	24-32 hours after Orientation Visit (morning admission)
5B Hospital Study Day 2	24 hours- 1-week after H-SD1 (morning admission)

5 STUDY IDS

Study IDs will first be assigned at the time of the REDCap online survey. This ID will start with "TRC" to represent "Tobacco Research Center". This ID will be placed on the eligibility checklist. At the time of consent, a study ID will be assigned beginning with the four digit 5B study research number and followed sequentially starting with 001. For example, the first person consented into the study will be given the ID, 8223-001. This ID will be added to the eligibility checklist and a screening log in Excel will store this ID.

6 STUDY PROCEDURES & VISITS

6.1 COVID-19 Screening

Prior to booking any participant for **any** in-person visit, we will ask the following screening questions via Zoom or on the phone. The answer must be "NO" to all of them; otherwise, they will need to be rescheduled.

1. Have you had any of the following symptoms in the past 24 hours?
    - Fever (temp >37.8 C or 100 F)
    - Night sweats
    - Shaking/chills
    - Shortness of breath

- Cough
- Sore throat
- Body aches
- Loss of sense of smell or taste

2. In the past 14 days, have you had unprotected close contact (within 6 ft for more than 15 minutes at a time) with someone you know to be diagnosed with COVID-19?
   (We understand there may be situations in the community in which you may not know the status of strangers. Please answer to your best knowledge for those you do know, such as those with who have frequent contact)
3. Have you recently tested positive for COVID-19?

6.2 SCREENING VISIT

The schedule of procedures for the screening visit will occur across two visits. One will be a **remote visit via Zoom** and the other will be an **in-person visit.**

The following will occur prior or during **the remote visit**:

6.2.1 Consent Process

Upon booking the Screening Visit, CRC will initiate the Informed Consent process over the phone. The CRC will first determine interest and then send the participant the informed consent and PowerPoint to their email for their review. When the participant has had time to review, the CRC will utilize the phone script to engage in the consent discussion, reviewing the purpose, procedures, alternatives, benefits, risks and opportunity to ask questions. The CRC will also assess understanding by asking the participant to respond to questions about the study. This process will be documented on the informed consent documentation checklist.

If the participant would still like to be in the study, the CRC will explain that they do need the HIPPA form signed and will do that when the participant comes in for their in-person visit.

The consent form will be sent to the participant via DocuSign. Upon receiving e-signature from the participant, the CRC will sign the consent form.

The participant will be sent a REDCap survey link 24 hours before their remote visit and asked to complete questionnaires included in the Screening Packet before the remote visit is conducted.

At the remote visit, the CRC will first take time to answer any questions about the study that the participant may have.

6.2.2 Screening Packet

Participants will complete the following via their CRC during the remote visit or through the direct Electronic Data Capture (EDC) system. The personal data form and medical history will not be entered into the Electronic Data Capture (EDC) system, but remain source documents.

Personal Data Form [paper source]

- This section contains the participant's contact information as well as an Emergency Contact.

Medical History [paper source]

- This section contains information regarding the participant's medical history, including exclusionary medical and psychiatric conditions.
- If any symptoms are endorsed on the Medical History in Section 8, the CRC will follow up with the participant asking:
  - How often and when was the last time you experienced these symptoms?
  - Do you ever take medication for this? If so, how often?
- Notes on the Medical History follow-up will be recorded at the bottom of the last page of the form to be reviewed by the study team.

Demographics [direct EDC, sent 24 hrs before online screening visit**]**

- This section contains information regarding the participant's gender, age, ethnicity, race, and education

Use/History/Dependence [direct EDC, sent 24 hrs before online screening visit]

- This section contains information regarding participant's use of nicotine replacement therapy, tobacco and e-cigarette product use, and drug/alcohol use
- Embedded in this section are the following standardized questionnaires: Nicotine Dependence Syndrome Scale, Fagerstrom Test for Cigarette Dependence, Penn State Electronic Cigarette Dependence Index

The steps for administering and reviewing questionnaires are found in the "Administering Forms and Questionnaires SOP."

The following will occur during the **in-person visit**:

6.2.3 Consent Documents

The participant will be asked to sign the consent form (for an original copy to

give to the hospital) and two HIPPA forms (one for the Investigator and one for the hospital). These must be on source.

The HIPPA form must have "entire medical record" checked off in Section B and the optional activities of banking samples checked off & initialed in Section G. Participant will be presented with the Experimental Subjects Bill of Rights.

The e-consent form will be saved on the study server and held by the study team. The signed consent form will be given to 5B and kept at the CTSI.

6.2.4 Urine Collection

Approximately 150 mL of urine will be collected for a drug toxicology and pregnancy test (females only). If positive for illicit drugs without a valid prescription, the participant will be dismissed without payment. If positive for pregnancy, the participant will be dismissed and paid for the visit. The "Urine Toxicology Screen SOP" and "Pregnancy Screen SOP" are references for these testing processes.

6.2.5 Physiological Measures

The following physiological measures will be assessed:

- Height and Weight
- Blood pressure and heart rate

Out-of-range blood pressure and heart rates will be re-tested once via manual methods at the end of the visit. If still out of range, the participant will be deemed ineligible.

Steps for these assessments are found in the "Measuring Basic Vitals SOP."

6.2.6 Saliva Collection

Participants will provide approximately 20mL of saliva for cotinine analysis. The steps for the saliva collection are found in the "Saliva Collection SOP."

6.2.7 NicAlert

A NicAlert will be run in cases when the research team cannot wait for saliva cotinine results to come back from the lab. In this case, the NicAlert will serve as the primary cotinine eligibility criteria. Before running, these procedures should be checked by the project manager.

6.2.8 End of Screening Visit

At the end of the in-person screening visit, the participant will be asked to fill out a "Certificate of Participation" in order to receive compensation for the screening visit. The participant will be given a urine sample cup to take home. If eligible, they will provide a urine sample in this cup and bring in on the day of their orientation.

The participant will be dismissed and the CRC will inform them that they will be contacted in 1 week with eligibility results from the screening visit.

The participant's urine will be discarded and the CRC will store the participant's saliva in the freezer at the UCSF Tobacco Research Center lab. The saliva samples will be labeled with the Study ID and transferred to the Benowitz Lab at the end of the day on Wednesday afternoons. The CRC will complete a Screening Log on the Shared Lab Drive filling in information on the samples dropped off. Cotinine results will be expected the following Monday.

Participant Screening and Enrollment Log Passcode: [redacted]

6.3 ORIENTATION

After eligibility is determined, an Orientation visit will be conducted via Zoom. The orientation visit should be at least 24 hours before the first 5B study day. For example, if a participant was oriented on Monday at 12 noon, they should be booked to begin 5B visit on Wednesday morning. This is to ensure they have at least 1 full day to try the JUUL product.

At the remote orientation visit, the following will occur:

- The CRC will review with the participant 5B location, procedures and reminders to not use combusted marijuana and to not smoke from 10PM the night before their 5B admission
- Participants will watch a training video on JUUL
- Participants will be given two flavors to choose from (menthol and tobacco)
- Participants will collect approximately 150 mL of urine. This will be done at home right after the Zoom visit is complete. This will serve as Baseline total nicotine equivalents as a measure of usual daily intake of nicotine.
- Participants will conduct a "curb-side pick-up/drop off" their urine to be aliquoted into two 20mL vials; one vial pH adjusted.
- They will be given their own JUUL device and selected pods (1-2) to use for one whole day before the 5B admission. This will be done within the same day as the Zoom visit, the day before their 5B admission.
- If CTSI CRS is available during the orientation, participant and CRC will go to 5B for nurses to conduct a quick vein check. This is for the nurses to inspect the participant's veins and ensure a successful access the morning of the study.
- Participants will be randomized, using a Latin square design, to distinguish which ARM the participant will start off first for Hospital Study Day 1.

Latin square design:

Participant #	Sequence	Period 1	Period 2
1	A	JUUL	Tobacco
2	B	Tobacco	JUUL
3	A	JUUL	Tobacco
4	A	JUUL	Tobacco
5	B	Tobacco	JUUL
6	B	Tobacco	JUUL
7	B	Tobacco	JUUL
8	A	JUUL	Tobacco
9	A	JUUL	Tobacco
10	B	Tobacco	JUUL
11	A	JUUL	Tobacco
12	A	JUUL	Tobacco
13	B	Tobacco	JUUL
14	A	JUUL	Tobacco
15	B	Tobacco	JUUL
16	B	Tobacco	JUUL
17	A	JUUL	Tobacco
18	A	JUUL	Tobacco
19	B	Tobacco	JUUL
20	A	JUUL	Tobacco
21	B	Tobacco	JUUL
22	B	Tobacco	JUUL

23	A	JUUL	Tobacco
24	B	Tobacco	JUUL
25	A	JUUL	Tobacco
26	A	JUUL	Tobacco
27	B	Tobacco	JUUL
28	B	Tobacco	JUUL
29	A	JUUL	Tobacco
30	B	Tobacco	JUUL
31	B	Tobacco	JUUL
32	A	JUUL	Tobacco
33	B	Tobacco	JUUL
34	A	JUUL	Tobacco
35	B	Tobacco	JUUL
36	A	JUUL	Tobacco
37	B	Tobacco	JUUL
38	A	JUUL	Tobacco
39	B	Tobacco	JUUL
40	A	JUUL	Tobacco

6.4 RT-PCR COVID-19 Testing Requirement

CTSI COVID-19 protocols will be followed.. If the participant has a positive result, they will not be able to participate at that time. Current guidelines typically include remaining in self-quarantine or seeking further care with a provider, should symptoms appear or worsen. We will ask that participants re-test no earlier than 14 days after the initial confirmed positive result. If the re-test is confirmed negative, we will allow that subject to participate in the study.

6.5 HOSPITAL STUDY DAY 1

Participants will be admitted to the hospital research ward the morning of their study visit at approximately 8am. Participants will be in a hospital-approved smoking room with negative pressure and a fan ventilating to the outside.

The below describes procedures if Hospital Study Day 1 assignment was the JUUL e-cigarette.

Pre PK – Baseline Assessments

- At 8 AM, the participant will be admitted to the research ward
- First morning urine void will occur at 8 AM and participant will be hydrated
- Breakfast will be served between 8:30-9:00 AM
- Expired CO will be measured to ensure the participant did not smoke any tobacco cigarettes
    - If the expired CO is ≤5ppm, the participant will receive a $50 cash bonus
    - If the expired CO is >5ppm, the CRC must notify the PI (or co-I's) immediately. A decision on how to proceed will be based on PI discretion.
- At about 9 AM, an intravenous catheter will be placed in the forearm for blood sampling
- **Baseline questionnaires** will be collected after IV placement: MNWS, QSU ("no cig")
- CRC will weigh the JUUL e-cigarette with the pod in the device pre-vaping
- At approximately 9:15 AM, a blood sample will be collected for **baseline plasma nicotine**
- At approximately 9:15 AM, a blood sample will be collected for **baseline plasma catecholamines**
- At approximately 9:15 AM, a urine sample will be collected for **baseline total nicotine equivalents and VOC measurements**
- At approximately 9:15 AM, a heart rate and blood pressure will be measured 10 minutes before vaping session
- At approximately 9:24, a heart rate and blood pressure will be measured 1 minute before vaping session

Standardized JUUL Vaping Session (9:25:30 AM – 12 PM)

- At 9:25:30 AM, participants will vape the JUUL e-cigarette: ***one 3.5-second puff every 30-seconds for a total of 10 puffs.***

- **Questionnaires** administered during the standardized session: Henningfield Drug Liking Assessment
- **Skin blood flow** will be measured by laser Doppler Velocimetry. The probe will be placed on the right foot. Measurements will be taken 10 minutes before the standardized session, 5 minutes after the last puff, and 30 minutes after the last puff.

PK Collection

- The CRC will weigh the JUUL after the puffing protocol is complete
- Blood samples will be collected at 2, 5, 7, 10, 15, 30, 60, 90, 118 minutes post end vaping session for **plasma nicotine**
- **Heart rate** will be collected at 2, 5, 7, 10, 15, 30, 45, 60, 75, 90, 100, 118 minutes post end vaping session
- **Blood pressure** will be collected at 5, 10, 15, 30, 45, 60, 75, 90, 100, 118 minutes post end vaping session
- Blood sample will be collected at 5 minutes post end vaping session for **plasma catecholamines**
- Urine Sample will be collected at 118 minutes post end of vaping session
- **Questionnaires** administered at **5, 10, 15, 30, 45, 60, and 120 minutes** post end vaping session: Henningfield Drug Liking Assessment; **5 minutes** post end vaping session: MNWS, QSU, mCES; **118 minutes** post end vaping session: MNWS, QSU("no cig")
- Lunch will be served around 11:30 AM, following the 118 min blood draw

Ad Lib Use (12 PM – 4 PM)

- At approximately 12:00 PM , a 4 hour ad lib video taped session will begin and participants will be allowed to use the JUUL as they wish
- CRC will weigh the JUUL e-cigarette before ad lib begins
- **Questionnaires** administered half-way through ad lib at approximately **1:30 PM**: MNWS, QSU, mCES; **5, 10, 15, 30, 45, 60, and 120 minutes** post ad lib start: Henningfield Drug Liking Assessment
- Blood samples will be collected every 30 minutes during ad lib at 12:30 PM, 1:00 PM, 1:30 PM, 2:00 PM, 2:30 PM, 3:00 PM, 3:30 PM & 4:00 PM for **plasma nicotine**
- Urine Sample will be collected at 195 minutes into Ad Lib session
- **Final questionnaires** administered at 3:50 PM: MNWS, QSU, mCES,Overall Drug Liking Assessment, GRPQ for JUUL, Utility of E-Cigs Questionnaire
- CRC obtains final weight of JUUL e-cigarette
- At 4:00pm the participant is discharged from the hospital ward

6.6 HOSPITAL STUDY DAY 2

In most cases, hospital study day 2 will occur directly after study day 1, however if it is more convenient for the participant to reschedule to a later time, they can complete study day 2 between 2 days and up to one week from study day 1. **The below describes procedures if Hospital Study Day 1 assignment was the JUUL vaping.**

The tobacco cigarette ARM will differ from the JUUL e-cigarette ARM in the following ways:

Pre PK – Baseline Assessments

- CRC will weigh the tobacco cigarette before smoking

Standardized Smoking Session

- At 9:25:30 AM, participants will smoke their usual tobacco cigarette: ***one 3.5-second puff every 30-seconds for a total of 10 puffs.***
- **Questionnaires** administered during the standardized session: Henningfield Drug Liking Assessment

PK Collection

- The CRC will weigh the cigarette butt after smoking is complete

Ad Lib Use

- CRC will provide tobacco cigarettes based on participant's normal brand and cigarettes per day
- CRC will weigh a standard reference tobacco cigarette before ad lib begins
- CRC obtains final weight of all tobacco cigarette butts
- At the end of the day, **final questionnaires** will be administered: Overall Drug Liking Assessment, GRPQ for tobacco cigarettes
- Regardless of which product was assigned, on Hospital Study Visit 2, the participant will also take the following as part of their final questionnaires: Difficulty Quitting, Purchase Tasks, Stiles Intent to Use Product Again

6.7 PARTICIPANT COMPENSATION

Below describes the participant compensation schedule for this study.

	Screening Visit	COVID-19 RT PCR Test	Hospital Study Visit 1	Hospital Study Visit 2	Completion Bonus
Compensation	**$30**	**$20**	**$350**	**$350**	**$100**
Type	Check	Check	$300 – check $50 – cash (for Expired CO ≤5ppm)	$300 – check $50 – cash (for Expired CO ≤5ppm)	cash
Processing Time point	After saliva cotinine results	After COVID test result	In final check (unless dropout)	In final check	At end of final visit
Total possible compensation	$30	$50	$400	$750	**$850**

7 DUTIES AND RESPONSIBILITIES OF STAFF

The Principal Investigator is responsible for study design and oversight of implementation, data analysis, and manuscript preparation.

The Co-Principal Investigators are responsible for study design and oversight of implementation, data analysis, and manuscript preparation, with the assistance of the Principal Investigator.

The Medical Monitor is responsible for medical study chart review and eligibility determination, medical history and physical examination at ZSFG admissions, reviewing and determining relatedness of adverse events, and other medically related expertise.

The Clinical Research Coordinator will oversee study logistics including consenting and screening participants, conducting study visit procedures, coordinating outpatient admissions and procedures with nursing staff at the research ward, coordinating specimen testing with laboratory, overseeing participant reimbursement, maintaining study charts and data entry.