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THE ABUSE LIABILITY PROFILE OF AN UNFLAVORED, SUCRALOSE-SWEETENED, ELECTRONIC CIGARETTE IN COMBUSTIBLE CIGARETTE SMOKERS

Sarah F. Maloney
Virginia Commonwealth University

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

By: SARAH F. MALONEY
M.S. Virginia Commonwealth University, Spring, 2018

Director: Thomas Eissenberg, Ph.D.
Professor of Psychology
Department of Psychology and Center for the Study of Tobacco Products

Virginia Commonwealth University
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List of Abbreviations

ANOVA	analysis of variance
bpm	beats per minute
CO	carbon monoxide
IPI	inter-puff-interval
IRB	Institutional Review Board
min	minute(s)
mg	milligram
ng	nanogram (0.0000000001 grams)
NRT	nicotine replacement therapies
mL	milliliter
PG	propylene glycol
ppm	concentration in parts per million
VAS	visual analog scale
VG	vegetable glycerin
V	voltage
W	watts
Ω	ohm

Abstract

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Electronic cigarettes (ECIGs) are a novel class of tobacco products that aerosolize a liquid, often containing nicotine, into an aerosol that users inhale (Breland et al., 2017). ECIG popularity is increasing in the US (Gentzke et al., 2019), and the growing number of ECIG users reporting frequent, daily use suggests that these products may have combustible cigarette-like abuse liability. ECIG abuse liability could be influenced by factors that impact 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 likely influences ECIG abuse liability is flavor (Goldenson et al., 2019), and there are over 7,000 unique ECIG liquid flavors available on the US market (Zhu et al., 2014), many of which are sweet flavors. Not surprisingly, many of these liquids contain added sweeteners (Fagan et al., 2018; Hua et al., 2019; Kim et al., 2018; Miao, et al., 2016) such as sucralose. Perceived sweetness increases ECIG appeal (Goldenson et al., 2016; Kroemer et al., 2018) and thus may enhance ECIG abuse liability. The purpose of this study was to examine the effects of sucralose and nicotine in otherwise unflavored PG/VG ECIG liquid solutions, via a 30-watt (W) ECIG, using multiple measures predictive of abuse liability to provide a basic understanding of the effects of sweeteners and

perceived sweetness on ECIG abuse liability in reference to combustible cigarettes. Fourteen dependent smokers completed five independent study sessions that were within-subject, Latin-square ordered and were identical in regards to all aspects but the product used. In each session, participants abstained ≥ 12 hours from all nicotine and tobacco products, and were given either their own brand of combustible cigarettes (OB) or one of the four ECIG conditions. The same ECIG device was used for all four ECIG conditions (i.e., 30 W, KangerTech Subtank Mini with a 0.5 Ω coil) and was filled with either: 0 mg/mL nicotine, unsweetened liquid solution (U_0), 0 mg/mL nicotine, sucralose-sweetened liquid solution (S_0), 15 mg/mL nicotine, unsweetened liquid solution (U_15), or a 15 mg/mL nicotine, sucralose-sweetened liquid solution (S_15). Following a one-hour rest period, participants completed baseline subjective questionnaires and had blood samples taken to assess nicotine delivery following a 10-puff, directed bout during which participants' puffs were recorded to analyze puff behavior. Following the 10-puff, directed bout, a second blood sample was taken and participants filled out a battery of subjective questionnaires. Participants completed hypothetical purchase tasks and subjective questionnaires before and after completing a progressive-ratio task (PRT). Results indicated that overall, the OB condition had a higher abuse liability than the ECIG conditions examined. On average, the OB condition delivered a larger dose of nicotine to participants than the ECIG conditions that contained nicotine, and as a result the OB condition produced more pronounced subjective effects compared to the ECIG conditions. The ECIG conditions that contained liquid with 15 mg/mL nicotine delivered significantly more nicotine and produced greater drug effects and reductions in tobacco abstinence symptoms than the ECIG conditions without nicotine. The presence of sucralose in the liquid solution increased ECIG product appeal and participants' puff duration and puff volume during the 10-puff, directed bout. During the PRT, participants worked

significantly harder and earned more puffs in the OB condition, however, the number of puffs earned in the U_0 condition and the S_15 condition did not significantly differ from the OB condition. Generally, the ECIG conditions examined in this study had lower abuse liability than the OB condition. The results from this study suggest that the presence of sucralose and nicotine elevate ECIG abuse liability, and do so through different mechanisms; sucralose appears to influence abuse liability through product appeal, and nicotine appears to influence abuse liability through drug effects and tobacco abstinence symptom suppression. Policies that restrict or ban sucralose and other sweeteners from ECIGs may protect youth and young adult populations from initiating ECIG use, while preserving the potential for ECIGs to help smokers quit combustible cigarettes.

The Abuse Liability Profile of an Unflavored, Sucralose-Sweetened, Electronic Cigarette in Combustible Cigarette Smokers

Electronic cigarettes (ECIGs) are battery-powered devices that use a heating element to aerosolize a liquid; users inhale the resulting aerosol. ECIG liquids contain solvents (e.g., propylene glycol and vegetable glycerin), flavorants, and the dependence-producing, stimulant drug nicotine (Breland et al., 2017). Emerging evidence suggests that ECIGs are not a single product, but rather should be viewed as a heterogeneous product class with great variability in design features (e.g., electrical power; Rudy et al., 2017), liquid characteristics (e.g., nicotine concentration; flavor; solvent ratio; Breland et al., 2017; Spindle et al., 2018; Zhu et al., 2014), and, importantly, nicotine delivery profile (Dawkins & Corcoran, 2014; Farsalinos et al., 2014; Hiler et al., 2017; Vansickel et al., 2010; Vansickel & Eissenberg, 2013; Wagener et al., 2017). As a product class, ECIGs have increased in popularity since their release to the U.S. market in 2007 (Richardson et al., 2015). For example, from 2017 to 2018, ECIG use increased 78% among high school students and 49% among middle school students, such that in 2018, 21% of high school students and 5% of middle school students had used an ECIG in the past 30 days (Gentzke et al., 2019).

One factor that may contribute to the rapid increase of ECIG use among adults and youth is their abuse liability. Generally, abuse liability has been defined as the propensity for a drug to engender dependence in users and produce adverse consequences (Balster & Walsh, 2015; Henningfield & Keenan, 1993). The abuse liability of tobacco products, including ECIGs, is contingent on many factors such as the rate of nicotine delivery, sensory and subjective reinforcing effects, social acceptability, and product appeal (Balster & Walsh, 2015; Carter et al., 2009; Jaffe & Jaffe, 1989). These factors can influence abuse liability independently or

interdependently. Typically, with many psychoactive drugs that humans use repeatedly, as the dose and the rate of drug delivery increases, the rewarding effects (i.e., euphoric feelings) and the likelihood for the drug or drug product to be abused also increases (Jaffe & Jaffe, 1989; Henningfield et al., 1985; Henningfield & Keenan, 1993; Perkins et al., 1994). For example, combustible cigarettes deliver a dose of nicotine to the brain almost immediately after inhalation (Henningfield et al., 1993), creating rewarding effects (i.e., drug liking, heightened arousal, mild euphoria, reduced nicotine/tobacco abstinence symptoms; Benowitz, 1996; Henningfield et al., 1985; Pomerleau & Pomerleau, 1992; Watkins et al., 2000) that increase the likelihood of continued use despite the harmful effects of chronic smoking (USDHHS, 2014). Therefore, evaluating the rate and dose of a tobacco product's nicotine delivery is one of many methods to evaluate that product's abuse liability.

Studies examining ECIG nicotine delivery have found that some ECIGs are capable of delivering cigarette-like amounts of nicotine to users (Hiler et al., 2017; Wagener et al., 2017), which could be indicative of cigarette-like abuse liability. In addition to nicotine delivery, subjective effects measures have also been used to examine ECIGs (Dawkins & Corcoran, 2014; Dawkins et al., 2012; Goldenson et al., 2016; Hajek et al., 2018; Hiler et al., 2017; O'Connell et al., 2019; Perkins et al., 2017; Rüther et al., 2018; Spindle et al., 2017; Spindle et al., 2018; Vansickel et al., 2010; Vansickel & Eissenberg, 2013). Subjective effect measures that assess positive or aversive drug effects, drug liking, and nicotine/tobacco abstinence symptoms are useful indicators of abuse liability (Carter et al., 2009; Fischman & Foltin, 1991). In addition, behavioral tasks have been developed and validated to assess the abuse liability of tobacco products and have also been used to examine ECIGs (Audrain-McGovern et al., 2016; Barnes et al, 2017; Maloney et al., 2019; McPherson et al., 2016; Vansickel et al., 2012). Overall, the

results from the abuse liability literature suggests that, on average, the ECIGs examined had a lower abuse liability when compared to combustible cigarettes. However, some ECIG products were found to have a similar abuse liability to that of combustible cigarettes on certain measures (Barnes et al., 2017; Maloney et al., 2019; McPherson et al., 2016; Vansickel et al., 2012). Not all of these studies included a measure of nicotine delivery, and the absence of this measure makes interpreting other abuse liability outcomes difficult. Nicotine delivery likely plays a significant role in the likelihood that nicotine-dependent combustible cigarette smokers will use/abuse ECIGs. Thus, an examination of nicotine delivery in tandem with other measures predictive of abuse liability would provide a more comprehensive and multidimensional approach to examining ECIG abuse liability.

In addition to nicotine delivery, another factor that may contribute to ECIG abuse liability is ECIG liquid flavor. While some ECIG liquid 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). Not surprisingly, a common ingredient in sweet-flavored ECIGs are sweeteners (Fagan et al., 2018). Adding sweeteners to non-sweet-ECIG liquids has been found to increase the reinforcing effects of ECIGs (Kroemer et al., 2018). Thus, added sweeteners may contribute to the rapid uptake of ECIGs, perhaps by increasing their abuse liability. Unfortunately, there has been little research examining the extent to which sweeteners in ECIG liquids interact with liquid nicotine concentration to influence ECIG abuse liability. The current study begins to fill this literature gap. The sections below detail ECIG use prevalence in the United States, ECIG characteristics, and the current literature regarding ECIG abuse liability, including how abuse liability can be examined in ECIGs.

Electronic Cigarette Prevalence

Adult ECIG Use

ECIG use has increased in adults and youth. In 2014, 3.7% of adults reported being current ECIG users (someday or everyday use; Schoenborn & Gindi, 2015), that number increased to 4.5% in 2019 (someday or everyday use; Cornelius et al., 2020). Most adult ECIG users in 2019 were estimated to be current cigarette smokers (39.1%) or former cigarette smokers (37.9%), however, 20.8% were estimated to have never been cigarette-smokers (Mayer et al., 2020). Among current ECIG users who were former smokers, 83% reported using a device with a tank (a refillable reservoir that holds ECIG liquid), and many reported using nicotine-containing ECIG liquids (35% reported using 6 mg/mL, 20% reported using 12 mg/mL, and 19% reported using 18 mg/mL nicotine) compared to non-nicotine-containing ECIG liquids (5% reported using 0 mg/mL nicotine). Among these former smokers, 74% reported using fruit flavors, 44% reported using candy flavors, 23% reported using menthol flavors, and 15% reported using tobacco flavors (Berg, 2016). Similarly, never-smoking current ECIG users also reported using tank devices (77%), but a much smaller proportion reported using nicotine-containing ECIG liquids (i.e., 23% reported using 6 mg/mL; 12% reported using 12 mg/mL nicotine; and 8% reported using 18 mg/mL nicotine) compared to non-nicotine-containing ECIGs (35% reported using 0 mg/mL nicotine). Sweet flavors were also popular in never-smoking ECIG users, such that 80% reported using fruit flavors, 43% reported using candy flavors, 36% reported using menthol flavors, and 6% reported using tobacco (Berg, 2016). Former smokers and never-smokers differed in their nicotine preferences, possibly indicating differing motivations for ECIG use. In addition, younger adults reported higher rates of current and daily ECIG use compared to older adults. For example, in 2016, 51.2%, of current (past 30-

day) ECIG users reported being under the age of 35 years old (Mirbolouk et al., 2018). Unfortunately, the relationship between age and ECIG use extends further to youth.

Youth ECIG Use

Rates of current ECIG use are increasing among youth. In 2017, 12% of high school students were current (past 30-day) ECIG users and 3% of middle school students were current ECIG users (Wang et al., 2018). From 2017 to 2018, ECIG use increased 78% among high school students and 49% among middle school students, such that in 2018, 21% of high school students and 5% of middle school student had used an ECIG in the past 30 days (Gentzke et al., 2019). Youth ECIG rates have remained stable despite global disruptions in day-to-day life from COVID-19 that may have affected access and availability. In 2021, 11% of high school students were estimated that current (past 30-day) ECIG users and 3% of middle school students were current ECIG users (Wang et al., 2018).

In a smaller sample of high school students (N = 2,945), 36% reported being lifetime ECIG users (Krishnan-Sarin et al., 2019). The flavor reported most commonly among youth in a national sample of past 30-day ECIG users was fruit (55%), followed by candy (21%), other flavors (13%), and mint/menthol (6%; Schneller et al., 2018). In a sample of high school ECIG users, 84% endorsed lifetime use of at least one of four presented ECIG products; specifically, 25% reported using a cig-a-like (See Figure 1 for product type examples), 61% reported using a pen-style device, 64% reported using a pod-mod (i.e., JUUL), and 71% reported using a mod-style device (Krishnan-Sarin et al., 2019). Nicotine use was reported in all device types (51% in cig-a-like devices; 47% in pen-style devices; 80% in the pod-mod device; 56% in mod-style devices; Krishnan-Sarin et al., 2019). Furthermore, individuals often reported not knowing if they were using nicotine in their device (22% cig-a-like; 21% pen-style; 10% pod-mod device;

14% mod-style; Krishnan-Sarin et al., 2019). ECIG use among nicotine-naïve youth and adults is a serious public health concern because nicotine is an addictive psychoactive substance and can be detrimental to the developing brain (Dwyer et al., 2009). The stable rates of continued ECIG use among adults and the increasing rates of ECIG initiation and use among youth, many of whom were nicotine naïve, suggests that certain ECIG products and/or characteristics may have an elevated abuse liability, especially among youth. Comparing the nicotine delivery profile of ECIGs to tobacco products with established nicotine delivery profiles will provide important context to the understanding of the risk associated with ECIG use.

Nicotine

Nicotine plays a major role in the initiation and continued use of tobacco products (Benowitz, 1996; Henningfield & Keenan, 1993; Watkins et al., 2000; Tutka et al., 2005). Nicotine is a naturally occurring botanical insecticide produced in relatively large amounts by tobacco plants and is also produced in relatively much smaller amounts in tomatoes, potatoes, and eggplants (Benowitz et al., 2009; Siegmund et al., 1999). In humans and experimental animals, nicotine is an addictive, psychoactive stimulant that can produce pleasurable effects, as well as toxic effects after chronic and/or high acute exposure. Nicotine can be absorbed into the bloodstream through lungs, skin, gastrointestinal tract, buccal mucosa, and nasal mucosa (Meyer & Maurer, 2011). Once in the bloodstream, nicotine is carried throughout the body and binds to nicotinic acetylcholine receptors in the central and the peripheral nervous systems to release neurotransmitters (Benowitz, 2010; Tutka et al., 2005). Nicotinic acetylcholine receptors are found throughout the body in the autonomic ganglia, adrenal medulla, neuromuscular junctions, and the brain (Benowitz, 1996; Tutka et al., 2005). Once nicotine is absorbed into the bloodstream, nicotine passes the blood-brain barrier within 10-20 seconds and binds to receptors

in the brain (Benowitz, 1988; Oldendorf, 1974a; 1974b; Tutka et al., 2005). While there are many nicotinic acetylcholine receptor sites throughout the brain, the greatest number of receptor binding sites are located in the cortex, thalamus, interpeduncular nucleus, amygdala, septum, and brain stem (Benowitz, 1996).

Nicotinic acetylcholine receptors are ligand-gated ion channels that are located directly on the cell body or dendrite. When nicotine binds to these receptors, the channel opens allowing sodium or calcium to enter the cell, which after a certain threshold, activates an electrical signal (i.e., action potential) that causes the release of neurotransmitters in the synapse (Benowitz, 2010). While these receptor sites can release different neurotransmitters depending on the location and receptor specificity, much of the addictive properties of nicotine result from the release of dopamine (Benowitz, 1996), particularly, in the brain's mesolimbic pathway, ventral tegmental area, and the nucleus accumbens (Benowitz, 2010; Govind et al., 2009; Watkins et al., 2000).

The release of dopamine in these brain areas plays a critical role in the pleasurable effects of nicotine use (Benowitz, 1996; Wakins et al., 2000). These pleasurable effects include mild euphoria, increased energy, and heightened arousal (Benowitz, 1996; Pomerleau & Pomerleau, 1992; Stolerman & Jarvis, 1995). In addition, nicotine can elevate blood pressure and heart rate with acute exposure (Benowitz, 1996; Buchhalter et al., 2005; Hughes & Hatsukami, 1986). The strength of these pleasurable effects of nicotine is influenced by the amount (dose) and rate (speed) of nicotine that is delivered to the user. Large doses of nicotine and faster rates of nicotine delivery produce more intense rewarding effects in users (Jensen et al., 2016). The speed and the amount of nicotine that is absorbed into the body are largely influenced by the

route at which it is administered, discussed below. Chronic exposure to nicotine can lead to the development of nicotine dependence.

Nicotine Delivery

Intravenous Administration. Intravenous (IV) infusion of nicotine bypasses traditional forms of nicotine absorption and produces a rapid peak in venous plasma nicotine concentrations (Feyerabend et al., 1985; Rosenberg et al., 1980). In a sample of five male cigarette smokers, an intravenous dose of 25 μg/kg nicotine (~ 2 mg for a 180 lb. person) was administered over the course of one minute and resulted in plasma nicotine concentrations of an average of 23.0 ng/mL (Feyerabend et al., 1985). Intravenous administration of nicotine produces effects rapidly, such as increases in heart rate, blood pressure, skin temperature, arousal, and pleasant sensations (Rosenberg et al., 1980). Therefore, products with similar nicotine delivery profiles to these intravenous doses of nicotine will likely also produce similar effects. On the other end of the continuum, there are nicotine products, such as transdermal nicotine, that deliver nicotine at very slow rates and produce less pronounced effects.

Nicotine Replacement Therapies. Nicotine replacement therapies (NRT), particularly nicotine inhalers, nicotine gum, and nicotine patches, deliver nicotine gradually over time and produce mild effects (de Wit & Zacny, 1995; Schneider et al., 2001). Nicotine absorption from nicotine inhalers primarily occurs transmucosally in the mouth and throat, and not via the lungs (Bergstrom et al., 1995; Schneider et al., 2001). Thus, increases in plasma nicotine concentration after nicotine inhaler use are relatively low (Fiore et al., 2008; Schuh et al., 1997; West et al., 2000). Similarly, nicotine delivered from nicotine gum is absorbed via the buccal mucosa in the mouth. Nicotine delivered via nicotine gum is absorbed slowly over 20 to 30 minutes of chewing (Benowitz et al., 1987; Benowitz et al., 1988). Peak plasma nicotine concentrations after

chewing a single piece of nicotine gum have been observed between 5 ng/mL and 10 ng/mL depending on the dose of the gum (i.e., 2 mg nicotine gum and 4 mg nicotine gum; Benowitz et al., 1987; Benowitz et al., 1988). Nicotine gum was reported to produce weaker effects than combustible cigarette smoking (Benowtiz, 1996). Nicotine delivered via a transdermal nicotine patch is also gradual, even more so than nicotine gum. Plasma nicotine concentrations rise gradually and peak anywhere from 2.5 hours to 10 hours after patch application (Evans et al., 2006; Fant et al., 2000; Mulligan et al., 1990). Increases in plasma nicotine concentrations are dose-dependent (Evans et al., 2006; Fant et al., 2000). Specifically, peak plasma nicotine concentrations observed with the use of a 7 mg patch was on average 7.0 ng/mL, peak blood nicotine concentrations observed with the use of a 21 mg patch was on average 21.1 ng/mL, and peak nicotine concentrations observed with the use of two 21 mg patches (i.e., 42 mg) was on average 38.5 ng/mL (Evans et al., 2006). In comparison, nicotine absorbed through the nasal mucosa by means of nasal spray produces stronger, more rapid effects than other forms of NRT (Tutka et al., 2005). Depending on the dose, nicotine nasal spray has been demonstrated to deliver nicotine concentrations of upwards of 8.1 ng/mL following administration (Schneider et al., 1996; Schuh et al., 1997). On average, NRTs deliver nicotine more slowly than intravenous nicotine administration and other forms of traditional tobacco products.

Combustible Cigarettes. There are many different types of inhaled tobacco products: combustible cigarettes, cigars, cigarillos, little cigars, blunts, pipe tobacco, bidis (small, flavored Indian cigarettes), waterpipe (i.e., hookah, narghile, or shisha), heat-not-burn products (e.g., Ploom, IQOS, Accord, etc.), however, combustible tobacco cigarettes deliver nicotine more reliably and efficiently of all tobacco products currently on the market (Benowitz et al., 2009; with the possible exception of some ECIGs, see below). Of the various products on the market

that involve direct use of the tobacco plant (rather than tobacco-derived nicotine, as in an ECIG), cigarettes have been the only route of administration known to produce similar spikes in blood nicotine concentrations to that of intravenous nicotine administration (Henningfield & Keenan, 1993). The quick delivery of nicotine is possible because pulmonary absorption of nicotine is rapid (Tutka et al., 2005), and the high amounts of nicotine absorbed are presumably due to the large surface area of the alveoli and small airways in the lungs (Benowitz et al., 2009).

An average tobacco cigarette contains about 10-14 mg of nicotine and roughly 1 to 1.5 mg of nicotine is absorbed during smoking (Benowitz et al., 2009). After a single puff, nicotine can reach the brain within 10-20 seconds (Benowitz et al., 2009). A laboratory study examined nicotine delivery during cigarette smoking in a sample eight male smokers via arterial and venous blood sampling that occurred simultaneously. Results revealed significantly more nicotine in arterial blood samples following the first five minutes of smoking (e.g., average 52.6 ng/mL) compared to venous blood samples (e.g., average 23.2 ng/mL; Henningfield et al., 1993). The rapid delivery and absorption of nicotine allows smokers to perceive the effects of the nicotine almost instantly, thus affording them the ability to change their smoking behaviors (e.g., puff number, size, etc.) to acquire the desired effects and prevent aversive effects by keeping plasma nicotine concentrations at a tolerable level (Benowitz, 2010; Benowitz et al., 2009). In addition, clinical lab studies that have investigated the nicotine delivery profile of combustible cigarettes have found that following 10 puffs and/or 5 minutes of smoking (~1 cigarette) plasma nicotine concentrations increased from a baseline means of 0-2 ng/mL to post-bout means of 13-24 ng/mL (Hajek et al., 2017; Lopez et al., 2016; Maloney et al., 2019). Until recently, the nicotine delivery profile of intravenous administration and combustible tobacco cigarettes has been unmatched (Benowitz et al., 2009; Henningfield & Keenan, 1993). However, some ECIGs

have been found to deliver cigarette-like amounts of nicotine under certain conditions (Hajek et al., 2017; Hiler et al., 2017; Wagener et al., 2017).

ECIG Devices. ECIGs are often characterized by users according to their visual appearance, although these products may be better classified by their components and/or electrical power (Rudy et al., 2017). In terms of physical appearance (see Figure 1), small devices that resemble the shape and size of cigarettes are often called "cig-a-likes", and were some of the earliest ECIGs released to the market. For this reason, cig-a-likes are sometimes referred to as 'early' or 'first' generation devices. These devices can be disposable or rechargeable and often come with disposable prefilled "cartridges" or "cartomizers" (ECIG liquid reservoirs, typically cylinder shaped and opaque in color that also include a heating element) that screw onto the top of the battery. The heating elements in these cig-a-like type devices are often powered when the user begins inhaling/drawing on the mouthpiece. "Pod-mod" devices are a popular ECIG style, particularly among youth (Vogela et al., 2018; see Figure 1). Pod-mods are small devices that often resemble USB flash drives or credit cards and have small replaceable, prefilled cartridges called "pods" (i.e., ECIG liquid reservoir) that attach to the top of the device. These devices are rechargeable and the heater is powered when the user inhales on the mouthpiece or when the user presses a small button located on the device.

Slightly larger, "pen-style" ECIGs (see Figure 1) are longer than traditional cigarettes, are cylindrical, and have attachable cartomizers or tanks (i.e., refillable liquid reservoirs) that screw on top of a battery. These devices are sometimes referred to as "second generation" devices or "vape pens". These devices are rechargeable and the heater is activated via button press. Finally, advanced personal vaporizers (APVs) or mechanical "MOD" or "mod" devices have also increased in popularity (Krishnan-Sarin et al., 2019). APVs and mods are large devices that have

wide cylinder tanks or sometimes shallow “dripping” liquid reservoirs used to drip ECIG liquid on to the heating unit directly after a few puffs (Harrell & Eissenberg, 2018). These liquid reservoirs attach on top of a large cylinder- or often times box-shaped battery housing units that contain large rechargeable batteries. These devices are sometimes referred to as “third or fourth generation” devices, and are rechargeable, customizable, and are operated via button press. Other devices include “squonk-mods” or “bottom-feeders” that include a flexible ECIG liquid reservoir in the battery housing unit that can be squeezed by the user to force the ECIG liquid up into the heating element attached above, mimicking dripping ECIG liquid directly on the coil (Harrell & Eissenberg, 2018). Variable power devices allow users to change the power settings (i.e., wattage, volts, and/or resistance). Many of the devices described above (i.e., pen-style, MODs/ APVs) have these device features that allow users to modify power output. This list of ECIG devices is not exhaustive. A 2014 study found that there were 466 brands of ECIG devices on the market (Zhu et al., 2014), and the ECIG product class has continued to expand in recent years. Although these classifications of ECIG devices are useful for identifying styles of ECIG devices, other ECIG features, such as the device power and ECIG liquid characteristics, may offer a more informative description of the ECIG device and user experience. Device features, such as ECIG liquid nicotine concentration and device power, as well as, user experience or behavior (i.e., puffing topography), can be more informative when trying to understand an ECIGs nicotine delivery profile (Hiler et al., 2017; Talih et al., 2015; Wagener et al., 2017). However, a challenge to understanding the influence of power settings (i.e., wattage, voltage, resistance) is the limited knowledge of power setting by ECIG users, thus leading to unreliable reports of power (Rudy et al., 2017).

Figure 1. Various ECIG styles and devices. The top image displays the liquid reservoirs detached from the battery component and the bottom picture displays the device attached to the liquid reservoirs.

ECIG Device Power. Device power is known to affect ECIG nicotine yield (Shihadeh & Eissenberg, 2015) and likely also affects ECIG nicotine delivery (Farsalinos et al., 2014; Hiler et al., 2020; Rüther et al., 2018; Wagener et al., 2017). ECIG device power (measured in watts; W) is determined by the battery voltage (V) and device heater resistance (measured in ohms; Ω) that can be adjusted via device settings or modifications to device components (e.g., coil, battery, etc.; Breland et al., 2017). Differing ECIG trends have emerged among ECIG users. Some ECIG users reported using low-powered ECIGs (M = 26.6 W) with high-resistance heating elements (M = 1.3 Ω) and higher ECIG liquid nicotine concentrations (M = 8.9 mg/mL nicotine), while other ECIG users reported using high-powered ECIGs (M = 61.0 W) with low-resistance heating elements (M = 0.4 Ω) and lower nicotine concentration ECIG liquids (M = 3.3 mg/mL nicotine; Smets et al., 2019). Interestingly, ECIG users that reported using high-powered ECIG devices paired with lower ECIG liquid nicotine concentrations, also reported using over twice as much ECIG liquid (M = 62.9 mL/week) as the ECIG users who reported using low-powered ECIG devices paired with higher ECIG liquid nicotine concentrations (M = 21.8 mL/week; Smets et al., 2019). Similar ECIG use patterns were observed in a smaller convenience sample of ECIG users in a clinical laboratory study. Specifically, exclusive ECIG users of pen-style devices and mod-style devices were recruited to use their usual ECIG device and products in the laboratory (Wagener et al., 2017). The pen-style ECIGs were on average 8.6 W, compared to the mod-style ECIGs that were on average 71.6 W. The pen-style devices were paired with ECIG liquids that had a mean nicotine concentration of 22.3 mg/mL, compared to mod-style devices that were paired with ECIG liquids with a mean nicotine concentration of 4.1 mg/mL. Participants using the high-powered ECIGs filled with low nicotine concentration ECIG liquids reported consuming over double the amount ECIG liquid (M = 54.8 ml/week) relative to participants

using low-powered ECIGs filled with high nicotine concentration ECIG liquids (M = 22.0 ml/week; Wagener et al., 2017). Although the use of lower nicotine concentration ECIG liquids appears indicative of lower abuse liability, additional examinations of use behaviors as well as device features suggest that individuals who use lower levels of nicotine compensate by using more ECIG liquid. This increased consumption of ECIG liquid not only exposes ECIG users to more nicotine, but also exposures users to more toxicants (Smets et al., 2019). In the study that examined pen-style and mod-style ECIG users' device characteristics, nicotine delivery of the devices was also assessed and revealed that plasma nicotine concentrations increased following a 10-puff bout to a mean of 7.3 ng/mL in the pen-style group and to a mean of 17.5 ng/mL in the mod-style group (Wagener et al., 2017). This study is one of the first demonstrations that ECIGs are capable of increasing plasma nicotine concentrations to cigarettes-like amounts and at cigarette-like rates. Furthermore, this study provides important evidence about how power can influence nicotine delivery (all other things being equal, higher power leads to greater nicotine delivery). In addition to device power, ECIG liquid characteristics can also impact ECIG nicotine delivery.

ECIG Liquids. There are thousands of ECIG liquids that available to ECIG users (Zhu et al., 2014). These liquids can be purchased in bottles for users to refill their devices or they can be purchased in preloaded cartridges or pods. ECIG liquids contain solvents such as propylene glycol (PG) and vegetable glycerin (VG) that act as a vehicle to carry nicotine, flavorants, sweeteners, and other additives into the users' lungs (Breland et al., 2017; Fagan et al., 2018). ECIG liquids come in a variety of nicotine concentrations ranging from 0 mg/mL nicotine to at least as much as 69 mg/mL nicotine (Breland et al., 2017; Goniewicz et al., 2018; Talih et al., 2019). ECIG liquid nicotine concentration affects nicotine yield (i.e., the amount of nicotine

emitted from the mouth-end of the ECIG; Talih et al., 2015). A clinical laboratory study revealed a similar ECIG liquid concentration-dependent pattern of nicotine delivery in experienced ECIG users (0, 8, 18, 36 mg/mL nicotine; all other device and liquid characteristics held constant: 7.3-watt, pen-style device, 1000 mAh battery, and 1.5 Ω, dual-coil, 510-style cartomizer; Hiler et al., 2017). Specifically, after 10 puffs (30 seconds between each puff) the 8 mg/mL nicotine ECIG liquid condition increased participants' plasma nicotine concentrations by 8.2 ng/mL, the 18mg/mL nicotine ECIG liquid condition increased plasma nicotine concentrations by 13.0 ng/mL, and the 36 mg/mL nicotine condition increased plasma nicotine concentrations by 17.9 ng/mL (Hiler et al., 2017). This ECIG-liquid concentration-dependent pattern of nicotine delivery was also observed in ECIG-naïve cigarette smokers, though the magnitude of delivery was not as pronounced. That is, plasma nicotine concentrations did not increase significantly in the 8 mg/mL nicotine condition but did increase significantly in the 18 mg/mL condition by 6.2 ng/mL and in 36 mg/mL condition by 6.8 ng/mL (Hiler et al., 2017). This study demonstrates that ECIGs are capable of delivering cigarette-like doses of nicotine under certain conditions, such as using 36 mg/mL nicotine ECIG liquids in a ~7-watt device in experienced ECIG users (also see Wagener et al., 2017). However, cigarette-like doses of nicotine from ECIGs have yet to be observed in samples of ECIG-inexperienced cigarette smokers.

Freebase Nicotine versus Protonated Nicotine (Nicotine "Salts"). In addition to the range of nicotine concentrations, there are also different forms of nicotine: unprotonated (i.e., freebase) and protonated nicotine (also known as "nicotine salt"; O'Connell et al., 2019; El-Hellani et al., 2015). Freebase nicotine is a more volatile form of nicotine and is often rated as harsher to inhale relative to nicotine salt (Chen, 1976). Nicotine salts are the combination of nicotine and an acid, such as benzoic acid (O'Connell et al., 2019). In an industry-funded,

clinical research study of 15 adult smokers, researchers compared the nicotine delivery of five ECIG products: a pod-mod device (i.e., myblu; 350 mAh battery) containing a 25 mg/mL freebase nicotine pod, the same pod-mod device with a 16 mg/mL nicotine salt pod, a 25 mg/mL nicotine salt pod, and a 40 mg/mL nicotine salt pod, in addition to a pen-style device (i.e., blu PRO; 1100 mAh battery capacity) filled with 48 mg/mL nicotine salt ECIG liquid. Nicotine delivery was compared across products and to combustible cigarettes. Results from the plasma nicotine analysis indicated that combustible cigarettes delivered, on average, the most nicotine after ten puffs (mean nicotine concentration = 17.8 ng/mL nicotine), followed by the pod-mod device attached to the 40 mg/mL nicotine salt pod (M = 10.3 ng/mL nicotine), the 25 mg/mL nicotine salt pod (M = 7.6 ng/mL nicotine), the 16 mg/mL nicotine salt pod (M = 6.5 ng/mL nicotine), the 25 mg/mL freebase nicotine pod (M = 5.0 mg/mL nicotine), and the open-system, pen-style ECIG filled with 48 mg/mL nicotine salt ECIG liquid (M = 4.9 ng/mL nicotine; O'Connell et al., 2019). These results from a preliminary, industry-funded study suggests that nicotine salt liquids in an ECIG device can deliver nicotine efficiently to users, thus warranting further clinical investigation. Additional ECIG liquid characteristics, such as flavors, appear to also have an impact on ECIG nicotine delivery profile.

***ECIG Liquid Flavors*.** In addition to variations of nicotine form and concentrations, ECIG liquids also come in over 7,000 flavors (Zhu et al., 2014). These flavors fall into different categories that oftentimes overlap within a single ECIG liquid. There are traditional tobacco flavors such as tobacco and menthol flavored ECIG liquids as well as the more popular sweet-flavored ECIG liquids (Berg, 2016). Sweet-ECIG liquids come in flavors such as fruit, candy, dessert, beverage, spice, and cream. Flavor appears to have an effect on nicotine delivery, either directly by influencing the chemical properties of the liquid (e.g., pH) and thus it's

pharmacokinetics (i.e., nicotine absorption, bioavailability, distribution, metabolism, and excretion of nicotine), or indirectly by influencing user sensory perception and product liking, and thus puffing behaviors (i.e., puffing topography). A 2017 clinical laboratory study examined the effect of flavor on ECIG nicotine intake in a sample of experienced ECIG users (St. Helen et al., 2017). Participants spent three days in an inpatient clinical laboratory and used a pen-style ECIG device (i.e., KangerTech 3.7 V, 1000 mAh battery with a KangerTech Mini ProTank 3 with a 1.5 Ω heater) filled with either strawberry (19.9 mg/mL nicotine; pH 8.3), tobacco (19.3 mg/mL; pH 9.10), or participants' usual flavor of ECIG liquid (average nicotine concentration 7.4 ± 3.4 mg/mL; average pH 6.80 ± 1.58). Participants took 15 puffs and then completed a 90-minute *ad libitum* use bout. Following the 15-puff bout, use of the strawberry flavored ECIG liquid resulted in a mean peak plasma nicotine concentration of 12.2 ng/mL, compared to plasma nicotine concentrations after using the tobacco-flavored ECIG liquid that was 9.5 ng/mL and the usual flavored ECIG liquid that was 6.2 ng/mL (St. Helen et al., 2017). This study demonstrates that ECIG nicotine delivery profile can be influenced by flavors, either directly by affecting the ECIG liquid composition or indirectly by increasing the number or the size of puffs as a result of product liking.

ECIG Liquid Sweeteners. A common theme among sweet flavor categories is that they represent sweet foods, and, in fact, sweeteners such as sucralose, glucose, fructose, sucrose, sorbitol, and ethyl maltol are common ingredients in ECIG liquids (Fagan et al., 2018; Hua et al., 2019; Kim et al., 2018; Miao et al., 2016). Sweeteners like sucrose and sucralose are added to ECIG liquids to sweeten the taste of the ECIG aerosol, while sugar alcohols, such as ethyl maltol, are used to sweeten the smell of the ECIG aerosols (Kim et al., 2018; Tierney et al., 2016). Sugars have been used in tobacco products to reduce the irritation and bitter taste of

nicotine (Talhout et al., 2006) and sweeteners likely are being used in ECIGs in a similar manner (Fagan et al., 2018). Flavored tobacco products tend to be perceived more favorably than unflavored tobacco products (Feirman et al., 2016; Goldenson et al., 2019), and sweet flavors are among the most popular ECIG liquid flavors (Berg, 2016). Sweet-flavored ECIG use is associated with younger adults and youth (Berg, 2016; Feirman et al., 2016; Russell et al., 2018). Thus, sweet-flavored ECIG products likely are contributing to the rapid uptake of ECIG use among these groups and may be exposing individuals who otherwise would be nicotine-naïve to nicotine, a dependence-producing drug. The limited number of sweeteners compared to the hundreds of other flavorants and millions of potential flavor combinations suggests that understanding the role of sweet flavors in ECIG initiation and continued use is amenable to controlled study. Currently, there are no studies that examine the impact of sweeteners on ECIG nicotine delivery.

In summary, ECIG nicotine delivery is influenced by many different factors such as device power, ECIG liquid nicotine concentration, user experience level, and ECIG liquid flavors. Data on ECIG nicotine delivery is important for understanding the likelihood of ECIG abuse. Nicotine delivery profile is known to influence the positive and negative physiological and psychological effects of product use, thus playing a major role in the facilitation of product dependence (Benowitz, 1996).

Development of Nicotine Dependence

Nicotine delivery plays a critical role in the development of nicotine dependence (Benowitz, 1996). Early drug use is due to the initial reinforcing or rewarding effects that increase the likelihood that a user will repeat the drug taking behaviors to experience the rewarding effects again (Jones & Comer, 2013). After chronic use, patterns of dependence may

be established and the primary reason for using the drug is to prevent or alleviate unwanted effects from periods of drug abstinence. Nicotine dependence is thought largely to be responsible for the continued use of tobacco products despite the serious health consequences that result from chronic use (Benowitz, 2010). The role that two forms of reinforcement play in the initiation and development and maintenance of nicotine/tobacco dependence are discussed in further detail below.

The Role of Positive Reinforcement in Nicotine Dependence

The positive reinforcing effects of acute nicotine administration include mild euphoria, increased energy, heightened arousal, mood regulation, reduced stress and anxiety, and appetite suppression (Benowitz, 1996; Pomerleau & Pomerleau, 1992; Watkins et al., 2000). These subjective effects are often rated as pleasant in smokers and are referred to as positive reinforcing effects because they increase the likelihood of individuals smoking to experience the effects again. Positive reinforcement plays a critical role in the initiation of tobacco/nicotine products. However, tobacco products such as the nicotine inhaler or the nicotine patch that deliver little nicotine and/or deliver it gradually over time produce very weak if any reinforcing effects (Benowitz, 1996). Thus, individuals are less likely to use these products again. After repeated exposure to the drug to experience the positive effects, dependence can develop and a different type of reinforcement becomes important in sustaining tobacco use, negative reinforcement.

The Role of Negative Reinforcement in Nicotine Dependence

Humans adapt to repeated exposures of many different drugs, including nicotine. For example, neural networks affected by nicotine are strengthened from repeated exposure of nicotine and the brain increases, or upregulates, the number of nicotinic acetylcholine receptors

(Govind et al., 2009). In addition, the amount of dopamine and other neurotransmitters are decreased, or downregulated (Benowitz, 1996; Benowitz, 2010). Due to these adaptations to repeated nicotine exposure, when a dependent cigarette smoker abstains from smoking, there is an absence of nicotine present in the brain and neurotransmitters like dopamine are at lower-than-normal levels, causing aversive effects (Benowitz, 2010; van de Nobelen et al., 2016). Tobacco abstinent smokers report effects that include gastrointestinal discomfort, irritability, anxiety, frustration, restlessness, difficulty concentrating, and mood disturbance (Benowitz, 1996; Benowtiz, 2010; Hughes & Hatsukami, 1986; Watkins et al., 2000). These aversive abstinence symptoms can occur after acute (Buchhalter et al., 2005; Drobes & Tiffany, 1997; Hughes, 2007; Hughes & Hatsukami, 1986) and long-term tobacco abstinence (Gilbert et al., 1999). The reintroduction of nicotine, especially via the preferred form of tobacco, can alleviate many of these abstinence effects almost instantly, thus increasing the likelihood of individuals smoking/using tobacco again to experience relief from nicotine/tobacco abstinence symptoms (Benowitz, 2010). Once dependence has been established, smoking to avoid or alleviate negative abstinence effects – a form of negative reinforcement – plays a vital role in continued, compulsive tobacco use (Carter et al., 2009).

Non-Nicotine Forms of Reinforcement

In addition to the reinforcing effects of the drug itself, other stimuli associated with the smoking process (e.g., the sight, smell, taste, and feel of smoke) become reinforcing after they have been paired repeatedly with the nicotine administration and its accompanying positive and negative reinforcing effects (Benowitz, 2010; Caggiula et al., 2002a; Caggiula et al., 2002b; Donny et al., 2003; Henningfield & Keenan, 1993). The repeated pairing of environmental stimuli and drug effects becomes a learned association through classical conditioning. In this

type of learning, a neutral stimuli becomes a conditioned or a learned cue for drug use which can lead to an individual or animal to engage in operant responding (i.e., self-administration of a drug in the context of positive and negative reinforcement; Caggiula et al., 2002a; Caggiula et al., 2002b; Caggiula et al., 2002c; Donny et al., 2003), and furthermore conditioned cues can cause relapse (Benowitz, 2010; Caggiula et al., 2002b). In addition to smoking-related cues, sensory factors play a significant role in smoking satisfaction (Rose, 2006). Indeed, in cigarette smokers, denicotinized cigarettes have been found to be both produce positive subjective effects and reduce nicotine/tobacco abstinence symptoms in smokers in a state of abstinence, even more so than nicotine administered via the intravenous route (Rose et al., 2010). The lack of smoking-related stimuli is thought to play a significant role in the low success rate of cessation with NRT products (Rose, 2006). In addition to the above-mentioned sensory factors, flavorings or flavorants, such as cocoa, licorice, menthol, or fruit extracts also serve as sensory stimuli for tobacco products (Budworth, 2019; Carter et al., 2009; Goldenson et al., 2019). These flavors can mask the aversive taste of nicotine and make tobacco smoke easier to inhale, and thus making the experience of smoking more pleasurable.

A recent study examined whether sweet taste and nicotine interact to enhance the rewarding effects of ECIGs. This study examined brain responses to the sight and smell of ECIGs with and without the addition of a sweetener and/or nicotine (Kroemer et al., 2018). Ten novel, non-sweet flavors were chosen (i.e., star fruit, lemongrass, dill pickle, anise, allspice, Cuban gold tobacco, lavender, jasmine, black pepper, and neroli) and sampled by participants without the addition of a sweetener or nicotine. Participants rated each flavor for harshness, sweetness, coolness, intensity, familiarity, wanting, and liking. The ratings were used to select equally liked flavors among the participants. Each of the flavors (equally liked by the remaining

10 participants) were randomized to one of four conditions: 1) flavor only, 2) flavor and sweetener, 3), flavor and nicotine, or 4) flavor, sweetener, and nicotine. Participants took each of the flavored ECIGs home to use (at least 20 puffs a day) for 2 days. After the at-home ECIG familiarization period, participants were placed into an fMRI scanner and fitted with a nasal mask that delivered ECIG aerosol odor of the four randomized flavors or an unexposed control ECIG flavor. There was a stronger response in the nucleus accumbens following the sight and smell of the sweet-paired ECIG flavor compared to the unexposed ECIG flavor, but this response was not significant for the sight or smell of the nicotine-paired ECIG flavor. Furthermore, the strongest responses in the nucleus accumbens occurred following exposure to the sweet- and nicotine-paired ECIG flavor, relative to control (Kroemer et al., 2018). These findings suggest that sweet taste can increase the reinforcing potential of ECIGs. The intensity of positive and negative reinforcement from nicotine and non-nicotine factors may increase ECIG abuse liability, or likelihood that individuals will use the drug product in excess, become dependent on it, and/or experience negative consequences as a result of its use (Balster & Walsh, 2015; Henningfield & Keenan, 1993).

Abuse Liability

The FDA defines abuse liability as the likelihood that a substance or drug product with psychoactive or central nervous system effects will sustain patterns of non-medical self-administration that results in disruptive or undesirable consequences (Balster & Bigelow, 2003; Carter & Griffiths, 2009). The harm associated with tobacco use comes from non-nicotine toxicant exposure primarily and is related to the frequency (e.g., cigarettes smoked per day) and the duration of use (e.g., years smoking; Carter et al., 2009). However, a tobacco product's abuse liability is influenced by many factors including the rate of nicotine delivery, sensory and

subjective reinforcing effects, social acceptability, and product appeal (see Figure 2; Balster & Walsh, 2015; Carter et al., 2009; Jaffe & Jaffe, 1989). These factors can influence abuse liability independently or interact to influence abuse liability. Typically, as the rate and the dose of psychoactive drug delivery increases, the rewarding effects (i.e., euphoric feelings) and the likelihood for that drug product to be abused also increases (Carter et al., 2009; Jaffe & Jaffe, 1989; Henningfield et al., 1985; Henningfield & Keenan, 1993; Perkins et al., 1994). Although abuse liability is largely influenced by a product's pharmacological properties, abuse liability is also influenced by sensory factors (e.g., smell, taste, feel, sight), contextual factors (e.g., coping with stress, drinking), environmental factors (e.g., bar, ease of availability), marketing factors (e.g., packaging, expectations), economic factors (e.g., price, taxes), social factors (e.g., social acceptance, peer use), regulatory factors (e.g., indoor-smoking policies; ECIG bans) and aversive effects (e.g., nausea; Balster & Walsh, 2015; Carter et al., 2009). Established methods have been developed and results from these assessments are used by the FDA and drug regulatory agencies to assess abuse liability in tobacco products, as well as other drug products (Carter et al., 2009). These studies are termed abuse liability assessments.

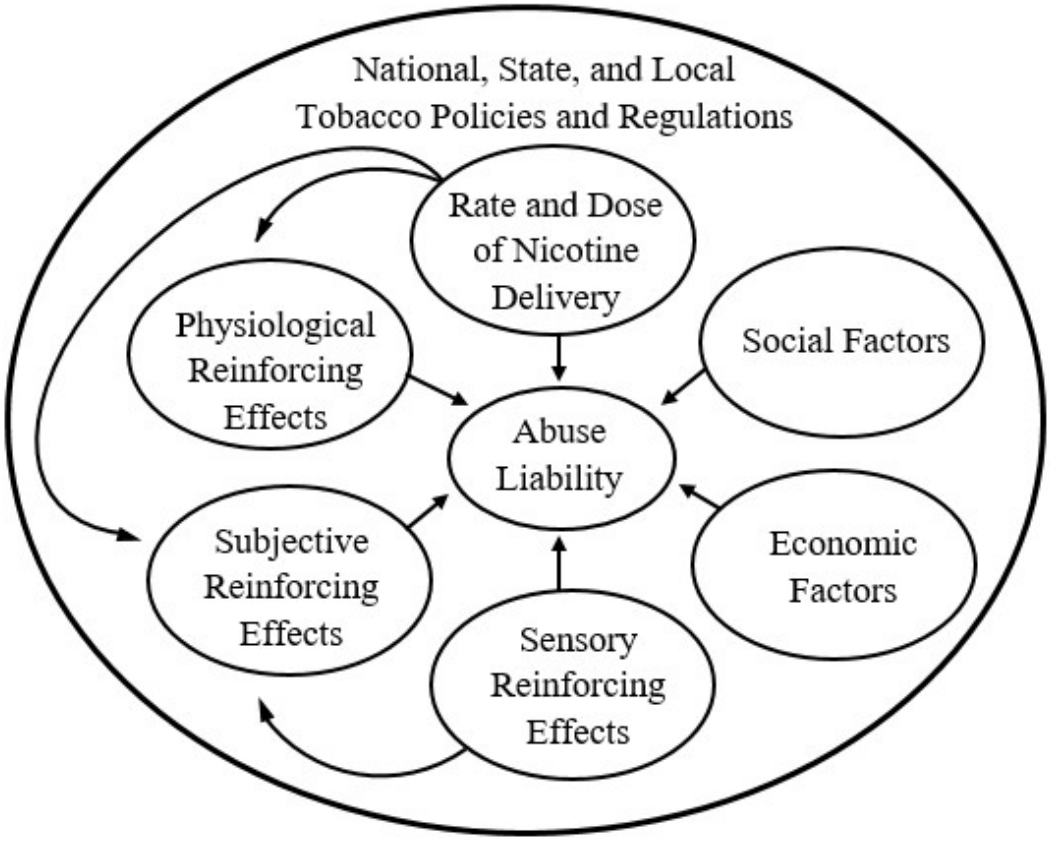

Figure 2. A conceptualization of various factors that impact abuse liability, with possible interactions between factors and within the confines of the current policies and regulations.

ECIG Abuse Liability Assessments

Abuse liability assessments aim to do two things, 1) determine the likelihood that individuals will engage in repeated use of a drug and become dependent on the drug/product, and 2) determine the likelihood that an individual will experience undesirable consequences as a result of the use of a drug/product (Carter et al., 2009). Abuse liability assessments can inform drug development, regulatory decisions, and clinical practices (Carter & Griffiths, 2009). Typically, abuse liability assessments are conducted with individuals that have histories of use with the drug of interest, such as smokers or experienced ECIG users, as these individuals' previous experiences provide context with which to rate the current drug experience in a laboratory setting (Carter & Griffiths, 2009). In addition, using smokers in abuse liability assessments of ECIG products increases the face validity of these experiments because smokers are more likely to use nicotine products (Carter & Griffiths, 2009), and nicotine products are often marketed to the adult smoking population (including ECIGs; Pearson et al., 2012; Abrams, 2012).

There are many different types of measures that can be used to assess abuse liability (Carter et al., 2009) that include: drug discrimination, acute dose-effect comparisons, examination of subjective effects, indices of tobacco withdrawal and craving suppression, self-administration procedures, choice procedures, and behavioral economic procedures (Carter et al., 2009; Fischman & Foltin, 1991). Ideally, abuse liability assessments are comprised of a combination of these measures in addition to examining nicotine delivery profile, to provide a comprehensive assessment of abuse liability. (Audrain-McGovern et al., 2016; Barnes et al., 2017; Gades et al., 2022; Maloney et al., 2019; McPherson et al., 2016; Stiles et al., 2017;

Vansickel et al., 2012), studies that examine ECIG nicotine delivery and/or acute subjective effects of ECIG use can also be useful for estimating abuse liability.

Pharmacokinetic Studies. The abuse liability of tobacco products is affected by nicotine pharmacokinetics and pharmacodynamics (e.g., Carter et al., 2009). Pharmacokinetics refers to the absorption, distribution, metabolism, and excretion of the drug. The pharmacokinetics of a drug/drug product has a direct influence on the pharmacodynamics of the drug/drug product, or the physiological effects and subjective effects that a drug produces. As discussed above, the nicotine delivery profiles of ECIGs vary and are influenced by device features, ECIG liquid characteristics, and ECIG-experience level. However, some ECIG device/liquid combinations are capable of delivering cigarette-like doses of nicotine in experienced users indicating that under some conditions, ECIGs may have cigarette-like abuse liability. This notion is explored further through evaluations of ECIG pharmacodynamics.

Subjective Effects. Subjective effects ratings are commonplace in human laboratory studies investigating the abuse liability of drugs (Fischman & Foltin, 1991). Subjective effects are individuals' reports of what they perceive before and after a drug product is administered and can include positive and negative reinforcing effects, as well as non-drug related reinforcing effects. Subjective effects measures can be used to evaluate a drug/drug products impact on an individual's reported mood, nicotine/tobacco abstinence symptoms, product liking and perceived positive and negative effects of product use. Key studies examining the subjective effects of ECIGs are described below.

Subjective Effects Related to Positive Reinforcement. Positive effects, like drug liking and drug appeal, are useful measures for understanding abuse liability and correlate with population indices of abuse (Carter et al., 2009). A clinical laboratory study investigated the

effect of ECIG liquid nicotine concentration (i.e., 0, 8, 18, 36 mg/mL nicotine) on ECIG nicotine delivery and ECIG subjective effects profile (Hiler et al., 2017). In each of the four sessions, participants sampled the ECIG and rated how satisfying they perceived the product to be (i.e., "Was the ECIG satisfying?"). Interestingly, smokers did not rate any of the nicotine-containing ECIGs as significantly more satisfying than the 0 mg/mL nicotine-containing ECIG (Hiler et al., 2017). In an industry study that examined the impact of ECIG nicotine concentration on subjective effects, researchers compared product liking of a 14 mg/mL, 29 mg/mL, and a 36 mg/mL cig-a-like style ECIG device (i.e., Vuse Solo) to participants' usual brand of cigarettes (positive control) and to 4 mg nicotine gum (negative control). On average, participants had lower product liking scores for the three ECIGs (means ratings ranged from 4.1 to 4.6; 10-point Likert scale) compared to their own brand of cigarettes (mean rating = 9.1; 10-point Likert scale), but participants had higher product rating scores for all of the ECIGs compared to the nicotine gum (mean rating = 3.2; 10-point Likert scale; Stiles et al., 2017). These studies demonstrate even at high nicotine concentrations, the ECIGs examined may not produce positive subjective effects of the same magnitude as combustible cigarettes, suggesting that these ECIGs have a lower potential for abuse than cigarettes in established cigarette smoking adults.

In addition, nicotine type (i.e., freebase or salt) may also influence the positive subjective effects of ECIGs. An industry study compared combustible cigarettes to freebase nicotine and nicotine salt ECIG liquids in various ECIG devices (i.e., a pod-mod device; myblu brand; 350 mAh battery with a 25 mg/mL freebase nicotine pod, a 16 mg/mL nicotine salt pod, a 25 mg/mL nicotine salt pod, and a 40 mg/mL nicotine salt pod, or a pen-style device; blu PRO brand; 1100 mAh battery capacity filled with 48 mg/mL nicotine salt ECIG liquid). Participants on average rated their own brand of cigarettes as most enjoyable (mean rating = 4.9; 7-point Likert scale),

followed by the pod-mod ECIG with 40 mg/mL nicotine salt pod (mean rating = 4.0; 7-point Likert scale), the pod-mod ECIG filled with lower nicotine salt pods (mean ratings = 3.5 for the 25 mg/mL and 16 mg/mL), and the freebase 16 mg/mL nicotine pod (mean rating = 3.2; O'Connell et al., 2019). Interestingly, the pod-mod device with the 40 mg/mL nicotine salt pod was rated, on average, as more enjoyable than the pen-style device filled with 48 mg/mL nicotine salt ECIG liquid (mean rating = 3.5; 7-point Likert scale; O'Connell et al., 2019). This study also suggests that, in smokers, combustible cigarettes are associated with more positive subjective effects than the ECIG devices and liquids examined in these studies. Thus, the ECIGs examined may also have a lower abuse liability than combustible cigarettes in smokers. However, the differences between the devices and ECIG liquid nicotine conditions in the study, coupled with the lack of data regarding the effects of nicotine salt liquids in the ECIG literature makes drawing conclusions about the differences between the ECIGs in this study speculative, and more work clearly is needed.

Another ECIG feature that impacts their subjective reinforcing effects is the use of flavors. A two-part, clinical abuse liability assessment examined the impact of reduced-harm messaging and ECIG flavor on measures of abuse liability, including subjective effects (Bono et al., 2019). In this study, the ECIG device features and liquid nicotine concentration were kept constant (all used a pen-style, "eGo" brand, 3.3 V ECIG battery attached to a 1.5 Ω dual-coil cartomizer filled with 36 mg/mL nicotine ECIG liquid solution) and ECIG liquid flavor varied: tobacco flavored versus menthol (Study 1), or cherry versus unflavored (Study 2). The results of this two-part study revealed that the menthol and cherry flavors increased ratings of pleasantness, taste satisfaction, and enjoyment of throat and chest sensations relative to tobacco and unflavored ECIGs in cigarette smokers. However, in comparison to participants' own brand of cigarettes

ratings of pleasantness, taste satisfaction, and enjoyment of throat and chest sensations were all significantly lower for all ECIG conditions (Bono et al., 2018). Again, this study demonstrates that the ECIGs examined appear to have a lower likelihood of abuse in cigarette smoking populations.

Flavors have also been demonstrated to have an impact on the subjective effects of ECIGs in samples of ECIG users. A clinical laboratory study examined the appeal of 20 different ECIG liquids, 10 flavors (i.e., six, sweet-flavored solutions: peach, watermelon, blackberry, cotton candy, cola and sweet lemon tea; three, non-sweet flavors: mint, tobacco and menthol; and one unflavored solution) at two different nicotine concentrations (i.e., 0 and 6 mg/mL nicotine) using an APV style ECIG (Joytech Delta 23 Atomizer attached to a Joytech eVic Supreme battery; Goldenson et al., 2016). Participants sampled each flavor and nicotine concentration combination and were asked to rate how much they liked each one. Overall, the sweet-flavored ECIG liquids received more positive ratings than the non-sweet flavors and the unflavored ECIG liquids (Goldenson et al., 2016). Interestingly, there were no effects of nicotine on any of the appeal ratings, besides throat hit, in this study (Goldenson et al., 2016), suggesting that sweet flavors may impact the subjective effects of ECIGs above and beyond nicotine in ECIG users. However, this study did not measure nicotine delivery. Therefore, drawing conclusions about the impact of nicotine on subjective effects is challenging as there is no way of knowing if nicotine was actually delivered, as these ECIGs are known to have variable nicotine delivery profiles.

Another study also used an ECIG-experienced sample (i.e., sole and dual ECIG users) to investigate the impact of flavor on the positive reinforcing effects of ECIGs (i.e., blu Tank cig-a-like style device attached to one of six flavored prefilled ECIG liquid cartomizers: Classic

Tobacco, Magnificent Menthol, Cherry Crush, Vivid Vanilla, Piña Colada and Peach Schnapps; all 12 mg/mL nicotine concentration; Kim et al., 2016). Results of this study revealed that ratings of perceived sweetness and coolness were associated with increased ratings of ECIG liking, while ratings of perceived harshness and bitterness were associated with decreased ratings of ECIG liking. Interesting, in this study, the impact of perceived sweetness on flavor liking was greater than the impact of perceived coolness (Kim et al., 2016). A recent study examined the impact of flavor concentration (i.e., 4.6% and 9.3% v/v cherry flavoring) and nicotine concentration (0, 6, and 12 mg/mL of nicotine; using a V2 Standard, cig-a-like style, 4.2 V ECIG device) on perceived sweetness, liking, and harshness in a sample of ECIG users (Pullicin et al., 2019). The non-nicotine-containing ECIG with 9.3% v/v cherry flavoring was liked the most. Nicotine decreased sweetness ratings and increased harshness ratings, possibly playing a role in participants' liking ratings (Pullicin et al., 2019). Together, these results suggest that perceived sweetness impacts the subjective effects of ECIGs and can be influenced by nicotine content, and therefore, should be investigated further as a potentially influential factor in ECIG abuse liability.

In a study that examined popular ECIG flavorants, individuals who were not current tobacco or ECIG users were recruited to sample popular ECIG flavorants diluted in PG/VG solvent solutions via small tubes (not delivered via ECIG device and without nicotine). After sampling the flavored solutions, participants rated perceptions of sweetness, pleasantness, and bitterness. The fruity flavorants increased ratings of sweetness but did not increase ratings of pleasantness. In an interesting contrast, the confection/dessert flavorants increased pleasantness ratings but not perceptions of sweetness. Finally, ethyl maltol was able to decrease bitterness ratings significantly (Rao et al., 2017). The results of this study are also consistent with the

notion that flavors and possibly sweeteners (e.g., ethyl maltol) may increase the positive subjective effects profile of ECIGs, and thus influence ECIG abuse liability.

In addition to flavorants and ethyl maltol, the ECIG sweetener sucralose has been examined. In this study, researchers examined the effects of adding the sweetener sucralose to commercially sweet-ECIG liquids and found that the addition of a sweetener to already sweet-ECIG liquids increased flavor liking of most of the examined flavors moderately (though increases were not significant statistically; Rosbrook et al., 2017). Together, these studies suggest that perceived sweetness is important for positive subjective effects, however increasing sweetness intensity does not seem to increase subjective effects above and beyond going from the absence of perceived sweetness to the presence of perceived sweetness. Additional research is needed to understand the impact that sweeteners have on the subjective experience of ECIG use. Furthermore, examining subjective effects related to negative reinforcement provides an additional dimension with which to understand ECIG abuse liability.

Subjective Effects Related to Negative Reinforcement. Nicotine dependence occurs over time and is a result of physical adaptations in response to repeated drug administration. However, when a tobacco-dependent individual abstains from using tobacco products there is a rapid decrease in the amount of nicotine in the body resulting in aversive nicotine/tobacco abstinence symptoms. The ability for a drug/drug product to relieve these abstinence symptoms in drug-dependent individuals suggests that the product may have abuse potential (Carter et al., 2009). A variety of instruments have been developed to measure nicotine/tobacco abstinence symptoms (e.g., Hughes & Hatsukami, 1986; Tiffany & Drobes, 1991) and many of them have been adapted to assess ECIGs.

Initial investigations found that early ECIG models (NJOY "NPRO" ECIG with 16 mg/mL nicotine concentration menthol or tobacco-flavored ECIG liquid and Crown Seven brand "Hydro" ECIG with 16 mg/mL nicotine concentration menthol- or tobacco-flavored ECIG liquid) were able to reduce nicotine/tobacco abstinence symptoms in smokers immediately following ECIG use (Vansickel et al., 2010). However, reductions in nicotine/tobacco abstinence symptoms were the greatest following own-brand cigarette use. The smaller magnitude of abstinence symptom suppression elicited by the ECIGs likely is a result of their lack of nicotine delivery, as indexed by concurrent measurement of plasma nicotine concentration in this study, and the observation that the ECIGs used delivered nicotine as effectively as an unlit tobacco cigarette (i.e., no measurable delivery; Vansickel et al., 2010).

In contrast, a clinical laboratory study compared the subjective effects profile and nicotine delivery of a pen-style ECIG (i.e., an "eGo" pen-style device with a 3.3 V, 1000 mAh battery attached to a 1.5 Ω, dual coil, 510-style cartomizer with 18 mg/mL nicotine ECIG tobacco or menthol flavored ECIG liquid) to a loose-leaf tobacco vaporizer and participants' own brand of combustible cigarettes and did not find that the ECIG examined reduced nicotine/tobacco abstinence symptoms significantly in cigarette smokers. Sample size (and therefore statistical power) may have been a concern in this study (i.e., N=15; Lopez et al., 2016). Interestingly, in this study the ECIG examined did deliver nicotine to smokers although the ECIG was on average less than participants' own brand of cigarettes and the loose-leaf tobacco vaporizer (Lopez et al., 2016).

In a comparison of device styles, nicotine abstinent smokers sampled two ECIG products (i.e., a Blu-Cig brand rechargeable cig-a-like with a 3.7 V, 80mAh battery capacity and output attached to a Blu Classic tobacco-flavored 16 mg/mL nicotine cartomizer, and a JoyeTech brand

"eGo C" pen-style device with a 3.2 V, 900mAh capacity battery, a 2.0 Ω heating element with tank cartridge filled with tobacco-flavored 16 mg/mL nicotine liquid) *ad libitum* for five minutes and rated their nicotine/tobacco abstinence symptoms before and after ECIG use. Reported nicotine/tobacco abstinence symptom ratings were reduced in both of the ECIG conditions, however, greater reductions were observed following use of the pen-style ECIG device compared to the cig-a-like style device (Lechner et al., 2015). However, this study did not examine ECIG nicotine delivery.

In a study of smokers, researchers compared the abuse liability profile of two ECIGs (0 and 36 mg/mL nicotine; pen-style, 3.3 V device, with either menthol or tobacco flavor) to participants' own brand of cigarettes and a medicinal nicotine inhaler. The 36 mg/mL nicotine ECIG reduced cravings and urges to smoke significantly after a five-minute (10-puff) bout. Interestingly, the 0 mg/mL nicotine ECIG also reduced intentions to smoke after the first five-minute (10-puff) bout, although ratings increased again following a brief period of abstinence (Maloney et al., 2019). However, the greatest reductions in nicotine/tobacco abstinence symptoms were observed after own-brand cigarette use, and in contrast, no significant reductions were observed at any time point after using the nicotine inhaler. This study suggests that ECIGs, with and without nicotine, are able to suppress nicotine/tobacco abstinence symptoms in smokers, and thus may reduce negative subjective effects. However, the nicotine-containing ECIG in this study and the nicotine-containing ECIGs in others studies (Dawkins et al., 2012; Perkins et al., 2017) were superior to non-nicotine-containing ECIGs in relieving nicotine/tobacco abstinence symptoms in smokers. Furthermore, while these reductions were on average less than participants' own brand of combustible cigarettes, they were larger than medicinal nicotine inhalers, suggesting that ECIGs are superior to the medicinal nicotine inhaler

for acute suppression of nicotine/tobacco abstinence symptoms. The results from these studies are consistent with the notion that the ECIGs used have, relative to combustible cigarettes, a moderate level of abuse liability in cigarette smokers.

ECIG liquid nicotine concentration is known to affect nicotine delivery and also has an effect on nicotine/tobacco abstinence symptoms in smokers and ECIG users. A clinical laboratory study examined the influence of nicotine concentration (i.e., 0, 8, 18, and 36 mg/mL) while keeping device characteristics constant (i.e., 7.3-watt, pen-style device, 1000 mAh battery, and 1.5 Ω, dual-coil, 510-style cartomizer). Results of this study revealed that 10 puffs from an ECIG that contained higher concentration ECIG liquid (i.e., 18 and 36 mg/mL) reduced nicotine/tobacco abstinence symptoms (i.e., urges to smoke, desire and intentions to smoke/use an ECIG) in smokers and ECIG users to a greater degree than the 0 mg/mL and the 8 mg/mL nicotine concentration ECIGs (Hiler et al., 2017). In a similar study, a pen-style ECIG (i.e., an "eGo" ECIG device with a 3.3 V, 1000 mAh battery attached to a 1.5 Ω, dual coil, 510-style cartomizer) was filled with three different nicotine concentration ECIG liquids (0, 18, 36 mg/mL, tobacco flavored) and was compared to smokers' own brand of cigarettes on measures of tobacco abstinence suppression. Participants' reports of smoking urge following two separate 10-puff bouts did not significantly decrease in any of the ECIG conditions, nor in participants own-brand cigarette condition. Sample size may also be a concern in this study (N =15; De La Garza et al., 2019). Together these studies suggest that factors beyond nicotine delivery may also be important for the reduction of nicotine/tobacco abstinence symptoms. Controlled studies that have examined the influence of ECIG liquid flavor on nicotine/tobacco abstinence symptom suppression in smokers (e.g., Bono et al., 2019; Cobb et al., 2019) and there are no clinical assessments of the effects of ECIG liquid sweeteners on nicotine/tobacco abstinence symptom

suppression. Given the high use rates of flavored ECIG liquids among smokers and the unifying feature of sweeteners suggests this is a viable research gap to explore.

Self-Administration. Self-administration studies are often considered a key method for understanding a drug's abuse liability and are considered the gold standard in animal models. (Benowitz, 1996; Carter & Griffiths, 2009). Generally, drugs that maintain recreational use in humans will maintain use in animal models (Hursh, 1991), including nicotine (Coen et al., 2009; Donny et al., 1999; Donny et al., 1995). Self-administration studies have high levels of face validity and predictive validity (Balster, 1991; Carter & Griffiths, 2009; Jones & Comer, 2013). In humans, self-administration studies use participants with histories of using the drug (e.g., heroin addicts, recreational cocaine users, ever- users of barbiturates and/or benzodiazepines, methamphetamine users, etc.; Comer et al., 1997; Cox et al., 2009; Griffiths et al., 1976; Kirkpatrick et al., 2012). For tobacco, these individuals are usually cigarette smokers and including them as participants allows comparisons of abuse liability across products that contain and are purported to deliver nicotine.

There are many human drug self-administration paradigms. They are similar in that they involve a controlled environment, provide participants the opportunity to self-administer a drug, often allow use behaviors to vary though sometimes also involve control over some behaviors (e.g., puff number; Barnes et al., 2017; Maloney et al., 2019; McPherson et al., 2016; Vansickel et al., 2012), and measure use patterns objectively (Henningfield et al., 1991). In addition to including pharmacokinetic and pharmacodynamic measures, self-administration studies typically have behavioral outcomes (Jones & Comer, 2013), such as the amount of the drug consumed (e.g., Audrain-McGovern et al., 2016; St. Helen et al., 2016; Wagener et al., 2017), rate of responding or effort participants are willing to exert for use of the drug (e.g., Audrain-McGovern

et al., 2016; Copp et al., 2015), and/or how often one drug is chosen over another drug or a placebo (e.g., Barnes et al., 2017; Maloney et al., 2019; McPherson et al., 2016; Vansickel et al., 2012). Additional measures used along with traditional abuse liability assessments, like nicotine delivery and puff topography, can also provide useful insight into the ECIG use experience and may be able to help describe the results on other measures of abuse liability.

Puffing Topography. Smokers are known to be able to manipulate the amount of nicotine they intake on a puff-by-puff basis (Benowitz et al., 2009; Tutka et al., 2005). There are numerous factors that influence nicotine intake, such as the number of puffs, puff duration, puff volume, depth of inhalation, and dilution of cigarette smoke with air (Benowitz et al., 2009; Tutka et al., 2005). These factors make estimating nicotine exposure of tobacco products using machine-generated nicotine yields difficult and at times inaccurate (Benowitz et al., 2009; Jarvis et al., 2001). For this reason, many studies have participants use tobacco products in laboratory settings to control intake parameters in an attempt to measure the nicotine delivery of 'equal' doses of each product (Carter et al., 2009). This control is often achieved by limiting the number of puffs, or the spacing of puffs, or duration of puffs (Carter et al., 2009). In recent years, new technology has been developed that allows for the unobtrusive measurement of ECIG user puffing behavior (Spindle et al., 2017). This technology is able to capture detailed puffing behaviors, such as puff volume, duration, and flow rate in addition to traditional measures such as puff count and inter-puff-interval (Hiler et al., 2017; Spindle et al., 2017). Puff topography measurement provides useful data for better understanding the smoking/ECIG use experience, such as nicotine delivery.

Puff topography measurement has helped reveal the relationships between ECIG experience level and ECIG nicotine delivery, ECIG liquid nicotine concentration and nicotine

delivery, and has recently been used to explore the relationship between ECIG flavor and nicotine delivery. Thus far, the literature suggests that ECIG-experienced users take longer (i.e., puff duration) and larger (i.e., puff volume) puffs than ECIG-inexperienced smokers (Hiler et al., 2017; Lee et al. 2015), and these differences likely underlie the observation that, after 10 puffs, ECIG-experienced users had higher plasma nicotine concentrations than ECIG-inexperienced smokers (Hiler et al., 2017). Furthermore, ECIG users and smokers were found to take shorter and smaller puffs when using high-nicotine concentration ECIG liquids (i.e., 18 and 36 mg/mL) compared to a non-nicotine-containing ECIG liquid (i.e., 0 mg/mL; Hiler et al., 2017). In addition, flavor has also been demonstrated to influence puff topography (St. Helen et al., 2018). For example, when using strawberry-flavored ECIG liquid, ECIG-experienced participants took longer puffs than when using tobacco-flavored ECIG liquid. Participants' puffs were the longest when they were using their usual-brand of ECIG liquid (St. Helen et al., 2018). These results suggest that preferred flavors are inhaled longer, indicating that flavor likely also influences the amount of aerosol the user inhales. Other studies examining the impact of flavor on puff topography have also provided evidence that flavor impacts puff volume and puff velocity (i.e., flow-rate; Robinson et al., 2018). Currently, there are no published studies investigating the impact of ECIG liquid sweeteners on ECIG puffing topography. Puffing topography measures are useful when examining ECIGs, especially when examining ECIG nicotine delivery because puffing topography outcomes provide context to how participants are obtaining more or less nicotine from certain ECIG devices. However, many self-administration studies do not include measures of puffing topography. Research involving ECIG self-administration methodologies are presented below in order of reinforcement paradigm.

Ad libitum Self-Administration. Clinical lab studies that use *ad libitum* puffing regimes usually report objective outcome measures such as puff count or amount of ECIG liquid consumed. Numerous *ad libitum* self-administration examinations of ECIGs have been conducted with ECIG-experienced users (e.g., Dawkins & Corcoran, 2014; Dawkins et al., 2016; Farsalinos et al., 2014; Spindle et al., 2017; St. Helen et al., 2016; St. Helen et al., 2017; St. Helen et al., 2018; Vansickel & Eissenberg, 2013; Wagener et al., 2017), while fewer examinations of *ad libitum* ECIG self-administration have been conducted with smokers and dual users (Audrain-McGovern et al., 2016; D'Ruiz et al., 2015; DeVito et al., 2019; Farsalinos et al., 2015; Hajek et al., 2017; Stiles et al., 2017; Yan & D'Ruiz, 2015).

A study that examined *ad libitum* self-administration of an APV-style ECIG device (i.e., 2600 mAh battery, with variable power setting capabilities set to 9 W) filled with 18 mg/mL nicotine ECIG liquid was examined over a 60-minute use period in smokers who were completely naïve to ECIGs and ECIG-experienced users (Farsalinos et al., 2015). Results revealed that participants took the same number of puffs across groups, but interestingly, ECIG-experienced users had significantly higher plasma nicotine concentrations at every time point during the 60-minute *ad libitum* bout compared to ECIG-naïve smokers. At first glance, these results may be perplexing, but the addition of puff topography measures in this study illustrates the utility of triangulating measures to allow researchers to go beyond speculation of user experience differences. Puff duration differed between ECIG-inexperienced smokers and ECIG-experienced users, such that smokers took shorter puffs (mean puff duration = 2.3 seconds) than ECIG-experienced users (mean puff duration = 3.5 seconds). Thus, puff duration likely influenced the differences in nicotine delivery profiles between smokers and ECIG users

(Farsalinos et al., 2015). Similar results have been found with controlled puffing parameters (Hiler et al., 2017).

Additionally, a study that examined of the impact of flavor on rewarding effects of ECIGs examined *ad libitum* self-administration of a sweet-flavored and unflavored ECIG liquid in cigarette smokers (Audrain-McGovern et al., 2016). A pen-style ECIG device with a refillable tank (i.e., "eGo" device, with a 650 mAh battery, with a 2.2.-2.4 Ω heating element) was filled with nicotine-containing ECIG liquid (i.e., either 6, 12, or 18 mg/mL nicotine based on participants' own-brand cigarettes nicotine level) that was unflavored or participants' preferred sweet flavor (i.e., either green apple or chocolate). Participants were presented with the two ECIGs simultaneously and were provided with a 90-minute *ad libitum* use period during which they could use as much or as little of each ECIG as they preferred. Results revealed a preference for the sweet-flavored ECIG over the unflavored ECIG. Participants took an average of 40 puffs from the sweet-flavored ECIG compared to 23 puffs from the unflavored ECIG (Audrain-McGovern et al., 2016).

A recent study examined the impact of flavor (i.e., unflavored, menthol, and fruit flavor) and nicotine concentration (i.e., 0 and 24 mg/mL) on ECIG appeal and self-administration in a sample of cigarette smokers (DeVito et al., 2019). Researchers provided participants with all six ECIG flavor and nicotine combinations simultaneously (i.e., Joyetch eVic Supreme, 9 W, APV-style ECIGs) simultaneously during two, 15-minute *ad libitum* product use bouts. Results revealed that participants took more puffs from the non-nicotine-containing ECIGs than the nicotine-containing ECIGs, but took the most puffs from the fruit-flavored, 0 mg/mL nicotine ECIG (DeVito et al., 2019). The results from these studies suggest that flavor can influence the frequency of self-administration of ECIGs. Factors that increase ECIG liquid consumption, like

flavor, can result in higher concentrations of plasma nicotine from increased ECIG liquid consumption, which can lead to a higher likelihood of continued use. Therefore, *ad libitum*, self-administration procedures are important in understanding a product's abuse liability as they provide insight into the absolute reinforcing efficacy of a product. In addition to *ad libitum* procedures, behavioral economics approaches have been applied to drug-administration procedures, thus providing another useful analytical tool for making comparisons across drug products.

Fixed- and Progressive-Ratio Procedures. A behavioral economic approach to measuring self-administration involves systematically varying experimental procedures to examine the amount of drug that is self-administered across a range of prices or effort (Carter et al., 2009). In fixed- and progressive-ratio self-administration paradigms, a certain amount of effort is required in order to earn access to the drug (i.e., button presses for puffs from a cigarette). Fixed-ratio schedules require the same number of responses to be made (e.g., 5 key presses) for the delivery of each reinforcer (e.g., a single puff of product) during a single session. Progressive-ratio schedules of reinforcement require increasing amounts of 'work' (i.e., button presses) for each reinforcement (i.e., puff) within a single session (Jones & Comer, 2013). After each puff is earned, a greater amount of work (i.e., button presses) is required to earn the next reinforcer (e.g., puff). Increases in work on progressive-ratio schedules of reinforcement are in an arithmetic or logarithmic fashion and are typically set within the confines of a specific time frame or until the participant decides to stop responding for the product (Carter et al., 2009). Fixed-ratio reinforcement schedules can also increase in work requirement but the work requirement is varied across sessions (Carter et al., 2009). Fixed-ratio schedules of reinforcement are common in animal models of self-administration. In contrast, progressive-ratio schedules of

reinforcement are often used in clinical models of self-administration (Carter et al., 2009; Giordano et al., 2001; Griffiths et al., 1979; Jones & Comer, 2013).

Progressive-ratio schedules of reinforcement are useful for examining the influence of price (i.e., amount of work/effort required per puff) on demand (i.e., amount of drug that is self-administered; Carter & Griffiths, 2009; Carter et al., 2009; Hursh & Winger, 1995). The primary outcome variable of progressive-ratio schedules is the 'breakpoint' or the point that participants stop responding for the drug (i.e., puffs; Carter et al., 2009; Giordano et al., 2001; Jones & Comer, 2013). The breakpoint can be used to compare across drug products. Drug products that participants are willing to work harder for (i.e., have larger breakpoint values) are considered to be more reinforcing and have a greater abuse liability (Jones & Comer, 2013).

A growing number of studies have used either fixed-, progressive-ratio, or co-current fixed- and progressive-ratio schedules of reinforcement to study ECIGs (Copp et al., 2015; Hoetger et al., 2021; Pacek et al., 2021). Studies that are most related to the current study are discussed. One study examined the influence of nicotine expectancies on self-administration in a sample of 21 ECIG-naïve cigarette smokers (Copp et al., 2015). Participants completed two experimental sessions during which they received nicotine-free, tobacco-flavored ECIGs and were asked to complete a progressive-ratio task (PRT). During one session participants were told that the ECIG contained nicotine and during the other session participants were told that ECIG was nicotine-free. The PRT was presented on a computer and required participants to push a key ten times to earn the first puff. The work requirement (i.e., key presses) increased by 30% for each subsequent puff. Female participants who reported perceiving ECIG nicotine content as extremely important for craving relief initiated self-administration of the ECIG sooner when they were told the ECIG contained nicotine, compared to when they were told the ECIG did not

contain nicotine. No other significant interactions or main effects were observed for breakpoint or any other PRT outcomes. This result suggests that, for some individuals, nicotine may be more important for initiating product use than for others, and therefore products that advertise nicotine or nicotine delivery may be more appealing and have a higher likelihood for abuse.

Another study used a fixed-ratio and a progressive-ratio schedule of reinforcement to examine the influence of flavor on ECIG self-administration (Audrain-McGovern et al., 2016). In this study, cigarette smokers sampled three flavored ECIG liquids (i.e., green apple, chocolate, and unflavored) and chose their favorite sweet flavor (i.e., green apple or chocolate) to use in the experimental sessions. ECIG liquid nicotine strength was matched to participants own brand of cigarettes and their smoking rate (i.e., 6, 12, 18 mg/mL nicotine) and ECIG liquids were administered via a pen-style ECIG device with a refillable tank (i.e., "eGo" device, with a 650 mAh battery, with a 2.2.-2.4 Ω heating element). Following 12 hours of nicotine abstinence, participants completed a computerized task with concurrent fixed- and progressive-ratio reinforcement schedules to earn puffs from the unflavored (fixed-ratio schedule of reinforcement) or the sweet-flavored ECIG (progressive-ratio schedule of reinforcement). Participants were told that they could switch from working on one of two screens, one that had a flavored icon (i.e., apple or piece of chocolate, representing the sweet flavor ECIG) and one that had an unflavored icon (i.e., a water droplet, representing the unflavored ECIG). The unflavored condition was on a fixed-ratio reinforcement schedule (each puff required 25 clicks of the unflavored icon) and the flavored ECIG was on a progressive-ratio schedule (each puff required 25 additional clicks on the icon than the previous puff earned; 25, 50, 75, 100, 125, ...etc). Instead of being reinforced after every 'earned' puff, participants were awarded points symbolizing puffs from either the flavored or the unflavored ECIG and were provided the

opportunity at the end of the session to take the number of earned puffs from each of the ECIGs. Results of this task revealed that participants were willing to work harder for puffs from the flavored ECIG than for puffs from the unflavored ECIG (Audrain-McGovern et al., 2016). This study suggested that sweet-flavored ECIGs will maintain self-administration at higher rates than unflavored ECIGs, and thus likely have a higher abuse liability. The individual and combined effects of nicotine and sweeteners in ECIG liquids have not been investigated systematically using progressive-ratio self-administration tasks.

Choice Procedures. Choice procedures require participants to choose between two options for reinforcement, for example choosing between using a product (e.g., puffs from a cigarette or ECIG) or money, or between using different drugs or drug products (Carter et al., 2009). When a multiple-choice procedure includes a monetary option, participants make discrete choices between a drug/drug product and increasing amounts of money. A choice (i.e., money or product use) is selected randomly and presented to the participant to keep or use. The main outcome of interest is the crossover point or the maximum dollar value that participants choose puffs of the product over money. This monetary value is used to understand the reinforcement of the drug in economic terms (i.e., dollar amount), and a higher crossover point suggests greater product reinforcement and thus greater abuse liability. To date, there have been five studies that have examined ECIG abuse liability using the multiple-choice procedure.

The first study to use the multiple-choice procedure to examine ECIG abuse liability compared an 18 mg/mL nicotine-containing ECIG to smokers' own brand of combustible cigarettes (Vansickel et al., 2012). In this study, smokers completed four sessions, one sampling session, and three experimental sessions. Participants were given one of three different multiple-choice procedures during which they were asked to make discrete choices between either: ECIG

puffs or increasing amounts of money; own-brand cigarette puffs or money; or puffs from their own brand of cigarettes or puffs from an ECIG. Results revealed that participants' own brand of cigarettes had a higher crossover point of $1.50 compared to the crossover point for ECIGs which was $1.06. Furthermore, a higher percentage of participants chose to receive own-brand cigarette puffs over ECIG puffs, suggesting that own-brand cigarettes have a higher abuse liability than the ECIG examined (Vansickel et al., 2012).

The second study that used the multiple-choice procedure also compared smokers' own brand of cigarettes to a ~ 24 mg/mL nicotine-containing, disposable ECIG (McPherson et al., 2016). In this study, participants completed four laboratory sessions: two sampling sessions where participants either used the ECIG or their own brand of cigarettes, and two experimental sessions with different choice paradigms (receiving puffs from the ECIG or money or receiving puffs from their own brand of cigarettes or money) using the multiple-choice procedure. Similar to the first study, participants' own brand of cigarettes had a significantly higher crossover point ($3.45) than the ECIG examined ($2.73), also suggesting that combustible cigarettes have a higher abuse liability than the ECIG examined in this study (McPherson et al., 2016).

A recent study used the multiple-choice procedure to examine the influence of nicotine on ECIG abuse liability compared to a positive and a negative control. This study compared a pen-style ECIG ("eGo" 3.3 V, 1.5 Ω device) filled with either 0 or 36 mg/mL nicotine ECIG liquid to smokers' own brand of cigarettes and a medicinal 4 mg nicotine inhaler (Maloney et al., 2019). Participants completed four sessions during which they first sampled study products and then completed a product-specific multiple-choice procedure (i.e., varying amounts of money or ECIG/cigarette/inhaler puffs). Similar to the first two studies, the crossover point for the nicotine-containing ECIG was significantly lower than for participants' own-brand cigarettes.

Interestingly, the crossover point for the 0 mg/mL nicotine ECIG condition did not differ significantly from that of participants' own-brand cigarettes. Furthermore, both ECIGs had a significantly higher crossover point than the nicotine inhaler (Maloney et al., 2019). The results of this study suggest that the multiple-choice procedure can be a useful tool for measuring the abuse liability of different nicotine-containing products.

A two-part study examined the influence of flavor (tobacco vs. menthol; cherry vs. unflavored) and reduced-harm messaging (reduced-harm message or reduced-carcinogen exposure message vs. no message) on ECIG abuse liability using the multiple-choice procedure in comparison to a positive control (i.e., own-brand cigarettes; Barnes et al., 2017). In this study, abstinent smokers came into the lab for one baseline session (own-brand cigarette use) and four experimental sessions that differed by product used and examined on the multiple-choice procedure. Results from the multiple-choice procedure indicated that the crossover points were lower for all ECIG conditions, except for tobacco-flavored ECIGs than own-brand cigarettes regardless of the presence or absence of reduced-harm messaging. Interestingly, the mean crossover point was higher for cherry-flavored than for unflavored ECIGs (Barnes et al., 2017). The results of this study demonstrate that flavor may also impact ECIG abuse liability.

Finally, the most recent study to assess ECIGs using the multiple-choice procedure examined the impact of varying ECIG liquid solvent ratios (i.e., PG/VG) on multiple-choice procedure crossover point in a sample of ECIG users. A 10-watt ECIG was filled with unflavored, 12 mg/mL nicotine ECIG liquid that was either one of five ECIG liquid solvent ratios: 100/0; 75/25; 50/50; 25/75; or 0/100% PG/VG. The results of this study did not reveal any differences between the ECIG conditions. Surprisingly, ECIG puffs were rarely chosen over even the smallest monetary option ($0.05) suggesting minimal reinforcement from the ECIGs

examined, and thus a low likelihood of self-administration and abuse of the liquids/device combinations used in this study (Harvanko et al., 2019). However, this study gave participants the choice between money and two or three puffs, as opposed to the previously mentioned studies during which participations were provided with the option of money or ten puffs of the session products, which may have influenced the results.

In summary, these clinical studies suggest that some ECIGs have a lower abuse liability than combustible cigarettes in smokers, as measured by the multiple-choice procedure (keeping in mind that very few ECIG devices/liquid combinations have been tested). In addition, the results from these studies also suggest that nicotine and flavor may also influence ECIG abuse liability. In addition to choice studies, purchase tasks also measure the reinforcing value of drugs/drug products using economic indices.

Purchase Tasks. There are many different types of purchase tasks used to estimate drug demand. Purchase tasks have been shown to be correlated with daily number of cigarettes smoked and nicotine dependence (Aston & Cassidy, 2019; Bickel et al., 2016), and therefore, are useful methods for measuring abuse liability. These tasks all utilize the law of demand: holding all else constant, increasing the price of a good decreases the quantity of the good demanded (and vice versa). There are simple purchase tasks, in which participants are given an allowance and may use it on products during a session. For example, one study presented lit own-brand cigarettes, own-brand ECIGs, and water behind a glass door to dual combustible cigarette/ECIG users and allowed participants to pay for access to the study product after completing measures of subjective craving. Participants could pay based on a range of prices ($0.01 to $0.25) with corresponding probabilities of unlocking the glass door to the product (from 5% to 95%). One choice was selected randomly and participants would either be granted access to the product or

not (Dowd & Tiffany, 2018). Results of this purchase task revealed that participants spent more money to gain access to tobacco cigarettes than ECIGs or water, suggesting that tobacco cigarettes have a higher reinforcing value and thus abuse liability than ECIGs in dual users.

More complex purchase tasks can be used to understand variations in demand as a function of varying factors (i.e., access to alternative products at varying prices and/or policy 'imposed' restrictions; Aston & Cassidy, 2019; Bickel et al., 1995; Bickel et al., 2018; Stein et al., 2018). These tasks allow for an estimate of the effect of the price of one product on the demand for another product, also known as cross-price elasticity. This discussion omits these more complex tasks in favor of the simpler version of the Cigarette Purchase Task (Jacobs & Bickel, 1999; MacKillop et al., 2008) that examines the demand of a single tobacco product (i.e., cigarettes) at systematically increasing prices, without the influence of another product's availability.

Cigarette Purchase Task. Behavioral economic procedures can also be used in hypothetical situations to estimate the abuse liability of a drug or drug products. The Cigarette Purchase Task (CPT; Jacobs & Bickel, 1999; MacKillop et al., 2008) is a hypothetical purchase tasks that is useful for estimating the reinforcing efficacy of a drug or product when traditional self-administration measures are unethical or brings about unnecessary risk (as in certain vulnerable populations, e.g., youth; Aston & Cassidy, 2019). In the CPT, participants state how many tobacco cigarettes they would hypothetically purchase and smoke in a single day (limited to their current budget) at increasing prices (outcomes are detailed below). The CPT and real-world cigarette purchases yield similar results (Wilson et al., 2016) and has been found to have construct and predictive validity (Aston & Cassidy, 2019). Study products may be sampled prior to completing the CPT or the CPT can be administered in the without sampling if participants

already are familiar with the products being examined (Aston & Cassidy, 2019). Furthermore, some studies have implemented actual reinforcement from the CPT by adding a choice-procedure component. Specifically, having participants choose a product/price at random or providing them with a study budget to use in a behavioral economic marketplace (Aston & Cassidy, 2019; Bickel et al., 2018; DeHart et al., 2019; Pope et al., 2019; Quisenberry et al., 2017).

Hypothetical, single-product CPT assessments produce several outcomes: demand curve, breakpoint, demand intensity, demand elasticity, Pmax and Omax. Demand intensity is the amount of hypothetical consumption when the product is free. The breakpoint is the price at which participants no longer report consuming the product (i.e., the corresponding product price when consumption is suppressed to zero; (Barnes et al., 2017). Omax is the most amount of money spent on the drug, Pmax is the corresponding price of the maximum expenditure on the drug. Demand elasticity refers to the change in consumption as a function of the change in price (i.e., how sensitive the demand of a product is to price; Bickel et al., 2016; Hursh, 1980). A demand curve is generated from the data to depict the quantity of demand as a function of price, to which the slope of the curve represents demand elasticity (Bickel et al., 2016). Outcomes from the CPT can be used to compare the reinforcing effects of different tobacco products (Carter et al., 2009). Below, studies examining ECIGs in cigarette smokers using the CPT are discussed.

In a comparison study of cigarettes and disposable ECIGs, smokers filled out three online versions of the CPT: cigarettes offered alone at increasing prices, disposable ECIGs offered alone at increasing prices, and cigarettes and ECIGs offered concurrently (i.e., cigarettes at increasing prices and disposable ECIGs at a fixed price; Snider et al., 2017). Participants' reported frequency of ECIG use was related to their cigarette and ECIG demand on the CPT.

Participants' who reported more frequent ECIG use had more elastic demand curves for cigarettes, such that these participants were more sensitive to increases in cigarette price and had a lower demand for cigarettes at higher prices than participants who reported less frequent or no ECIG use. Furthermore, participants with more frequent reported ECIG use had a higher demand for ECIGs when the ECIG was offered alone. When an ECIG was offered at a consistent price concurrently with increasing cigarette prices, participants who reported more frequent ECIG were more sensitive to increases in cigarette prices compared to individuals who reported little ECIG use, despite an alternative ECIG product. Interestingly, ECIG substitution during the concurrent CPT was observed in frequent and infrequent ECIG users (Snider et al., 2017).

In another study that used the CPT to examine ECIGs, smokers sampled nicotine-containing ECIGs that differed in flavor and reduced-harm messaging, as well as their own-brand cigarettes, and completed a variety of abuse liability measures, including the CPT (Barnes et al., Cobb, 2017; Bono et al., 2019). Participants in this study responded to a modified CPT in which they were asked how often they would take 10 puffs of the study products at increasing amounts of money. Responses on the CPT indicated that elasticity, or sensitivity of demand to price, was significantly higher in all the ECIG conditions compared to participants' own brand of cigarettes. That is, as the price increased, the demand for ECIGs decreased more rapidly than demand for their own brand of cigarettes, suggesting lower abuse liability. Results also demonstrated a significant effect of demand intensity, specifically, participants reported wanting six to nine times fewer 10-puff bouts with any ECIG compared to own-brand cigarettes when products were free (Barnes et al., 2017). Products that are inelastic to price changes, such as cigarettes in this study, indicate a higher likelihood for abuse. Furthermore, this study, like others (Snider et al., 2017) demonstrated that cigarettes have higher indices of reinforcement as

measured. Currently, no studies have examined the impact of ECIG liquid sweeteners using the CPT.

In summary, using a variety of abuse liability measures is important for a comprehensive abuse liability assessment. Examining the pharmacokinetic effects, subjective rewarding effects, self-administration behavior, and demand sensitivity of a tobacco product can help inform public health officials of the likelihood that individuals will abuse that product and what factors lead to increases and decreases in its abuse potential. Systematically manipulating variables such as liquid nicotine concentration or sweeteners can help to identify key factors that influence ECIG abuse liability.

Regulatory Implications

In 2009, the Family Smoking Prevention and Tobacco Control Act of the 111th Congress gave the FDA the broad authority to regulate the manufacture, distribution, and marketing of tobacco products with the goal of protecting public health. The FDA's authority was extended to ECIGs in May of 2016. The literature addressing how best to regulate ECIGs is growing, and comprehensive abuse liability assessments of ECIGs can inform this effort (Balster & Walsh, 2015; Carter & Griffiths, 2009). Due to the drastic increase in ECIG uptake among youth, the FDA has moved to stop the sale of flavored ECIG liquids in non-age-restricted locations and is considering a ban of all flavored ECIG products other than mint, menthol, and tobacco (Dyer, 2019). Systematic abuse liability assessments of ECIGs, especially those investigating the impact of characteristics known to influence abuse liability (i.e., nicotine delivery) and characteristics suspected of influencing ECIG abuse liability (i.e., sweeteners) would provide useful information for developing appropriate regulations, such as product standards regarding the use of sweeteners

in nicotine-containing ECIG liquids so they are not to be used as loop holes in the case of a flavor ban.

Statement of the Problem

ECIG use is increasing, especially among youth (Gentzke et al., 2019), suggesting that at least some ECIGs may have an elevated, and possibly cigarette-like abuse liability. However, the thousands of ECIG liquids that exist in the US market make clinical evaluations of abuse liability on individual products and flavors challenging. However, a common feature of sweet-flavored ECIG liquids is the use of sweeteners (Fagan et al., 2018). This common feature may also contribute to ECIG abuse liability and therefore is an important subject for empirical study and furthermore may be a potential regulatory target.

Statement of Purpose

The current study aimed to examine the effects of sucralose and nicotine in otherwise unflavored PG/VG ECIG liquid solutions, via a 30-watt ECIG, using multiple measures predictive of abuse liability assessments to provide a basic understanding of the effects of sweeteners and perceived sweetness on ECIG abuse liability in reference to combustible cigarettes. Studying the influence of sucralose alone and in combination with nicotine will help tease apart ECIG's pharmacological and sensory reinforcing effects. Furthermore, the numerous valid measures of abuse liability that were used in the current study will result in a comprehensive abuse liability assessment of the use of sucralose in ECIG liquids.

Statement of Hypotheses

Main Hypotheses

The main hypotheses of the current study were 1) the sweetened, 15 mg/mL ECIG liquid would be more reinforcing than the non-nicotine, unsweetened ECIG liquid as measured by a

progressive-ratio self-administration task (PRT), a modified CPT and cross-price CPT, and subjective measures, although participants' own-brand cigarettes would be the most reinforcing of all the products on these tasks, and 2) the nicotine-containing ECIG conditions would increase plasma nicotine concentrations significantly more than the 0 mg/mL nicotine ECIG liquids, but less than participants' own brand of cigarettes. See Table 1 for summarization of hypotheses by outcome measure.

Exploratory Hypotheses

The exploratory hypotheses of the current study were 1) the sweetened, 0 mg/mL nicotine ECIG liquid would be more reinforcing than the unsweetened, 0 and unsweetened, 15 mg/mL nicotine-containing ECIG liquids on subjective items suggestive of positive reinforcement (e.g., did the product taste good, did you enjoy using the product, etc.), but less reinforcing than the sweetened, 15 mg/mL ECIG liquid and participants' own-brand cigarettes, and 2) the unsweetened, 15 mg/mL nicotine-containing ECIG liquid would be more reinforcing than sweetened, 0 mg/mL and the unsweetened, 0 mg/mL ECIG liquids on measures suggestive of negative reinforcement (e.g., did the product relieve your craving for a cigarette, etc.), but less reinforcing than the sweetened, 15 mg/mL ECIG liquid and participants' own-brand of cigarettes. See Table 1 for summarization of exploratory hypotheses by outcome measure.

Table 1.

Summary of Study Hypotheses.

Outcome Measure	**Reinforcing Effects Hypothesis**
Plasma Nicotine	[OB] > [S_15] > [U_15] > (([S_0] & [U_0]))
Heart Rate	[OB] > (([S_15] & [U_15])) > (([S_0] & [U_0]))
Puff Topography	[OB] > [S_15] > [S_0] > [U_15] > [U_0]
Progressive-Ratio Task	[OB] > [S_15] > (([S_0] & [U_15])) > [U_0]
Cigarette Purchase Task	[OB] > [S_15] > (([S_0] & [U_15])) > [U_0]
Cross-Price CPT	[S_15] > (([S_0] & [U_15])) > [U_0]
Hughes & Hatsukami Tobacco Withdrawal Scale	[OB] > [S_15] > [U_15] > [S_0] > [U_0]
Questionnaire of smoking Urges-Brief	[OB] > [S_15] > [U_15] > [S_0] > [U_0]
Positive and Negative Affect Schedule	[OB] > [S_15] > [U_15] > [S_0] > [U_0]
Cigarette Evaluation Questionnaire	[OB] > [S_15] > (([S_0] & [U_15])) > [U_0]
Drug Effects Questionnaire	[OB] > [S_15] > [S_0] > [U_15] > [U_0]
Direct Effects of Nicotine Scale	[OB] > [S_15] > [U_15] > [S_0] > [U_0]
General Labeled Magnitude Scale	[OB] > [S_15] > [U_15] > [S_0] > [U_0]
Labeled Hedonic Scale	[OB] > [S_15] > [S_0] > [U_15] > [U_0]
Willingness to use again questionnaire	[OB] > [S_15] > [S_0] > [U_15] > [U_0]

Summary of the current study's main and exploratory hypotheses by outcome measure.

[U_0] Unsweetened, 0 mg/mL nicotine concentration ECIG liquid condition.

[U_15] Unsweetened, 15 mg/mL nicotine concentration ECIG liquid condition.

[S_0] Sweetened, 0 mg/mL nicotine concentration ECIG liquid condition.

[S_15] Sweetened, 15 mg/mL nicotine concentration ECIG liquid condition.

[OB] Participants' own-brand cigarettes purchased by the laboratory staff.

Method

Participant Selection

A total of 30 combustible cigarette smoking participants were needed to complete this study. To determine the sample size, multiple power analyses were conducted using G* Power (Faul et al., 2007) and effect size tables (Barcikowski & Robey, 1985) using previous studies' effect sizes for the main outcome measures for the current study: progressive-ratio task (PRT) outcome breakpoint, plasma nicotine concentration, subjective effects of nicotine, and nicotine/tobacco abstinence symptom suppression. 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). Results from these analyses determined that a total of 30 participants would be sufficient to have at least 80% power to detect a true effect.

Participants were recruited through word of mouth, local Craigslist advertisements, Facebook advertisements, Institutional Review Board (IRB) approved study fliers posted around local Richmond businesses, and via the clinical laboratory at the Center for the Study of Tobacco Products (CSTP) participant registry. All experimental sessions took place in the clinical laboratory of the CSTP located in between Virginia Commonwealth University's (VCU) medical campus and Monroe Park Campus. To be eligible to participate, all participants were required to be between the ages of 21 and 55, smoke eight or more cigarettes per day for at least one year,

have an expired CO ≥ 10 ppm or more at screening, have tried an ECIG at least once in their lifetime, and be willing to use an ECIG in the lab. Individuals who reported using an ECIG in the past 30 days or had intentions to quit smoking in the next 30 days were excluded. Individuals who reported needle phobia, any current 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), seizures, current diagnosed psychiatric conditions, current psychiatric treatment, or psychotropic medication use were excluded. Individuals who reported using cannabis > 15 days in the past 30 days, alcohol > 25 days out of the past 30 days, and any use of cocaine, opioids, benzodiazepines, and/or methamphetamine in the past month were excluded. Women were excluded if they reported breastfeeding or pregnancy, or if they tested positive for pregnancy (by urinalysis) at screening. Participants' blood pressure and weight were measured, and individuals with a systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90, or weight < 110 pounds were not be eligible to participate. Individuals with other reported current diagnosed medical conditions (e.g., diabetes, thyroid disease, Lyme disease) were considered for exclusion after consultation with the medical monitor. Participants with any medical condition and/or use of medication that may affect participant safety or study outcomes were excluded based on these consultations.

Screening and Informed Consent Procedures

Interested individuals completed a two-part screening procedure. The first part of the screening procedure was conducted over the phone with CSTP study personnel or on the internet via the CSTP secure website. This first part of the screening process included a description of the study procedure and a short questionnaire of voluntary information concerning health status,

tobacco use, ECIG use, alcohol use, and illicit drug use. Individuals who appeared eligible and who were interested in the study were scheduled for the second part of the screening procedure, an in-person screening visit at the CSTP. When individuals came into the CSTP for the in-person screening visit, they were seated in an individual session room and were provided with a copy of a study consent form. A research assistant asked potential participants to follow along as they read the consent form out loud or played a video recording discussing the consent form (see appendix A). Participants were able to stop the research assistant or video recording at any time to ask questions during the explanation of the study procedure. Individuals had the opportunity to review study procedures (i.e., tasks and questionnaires) that were used during the study sessions with the exception of blood sampling procedures. Once participants had a detailed understanding of the study procedures, they were given time to decide if they wanted to give consent to participate, decline to participate or reschedule their screening visit if they needed more time to decide.

Following written informed consent to participate in the study, participants completed several forms: The Health Information Questionnaire, the Fagerström Test for Cigarette Dependence (Fagerström, 2011; Heatherton et al., 1991), the Penn State Cigarette Dependence Index (Foulds et al., 2015), and a demographics questionnaire. Participants then had their heart rate and blood pressure measured, provided an expired air CO breath sample, and women provided a urine sample to be tested for pregnancy (Accutest Value hCG urine pregnancy test, Jant Pharmaceutical Corp). Eligible participants had their sessions scheduled according to the participants' preferences and availability. Reminder phone calls were made and/or reminder text messages were sent to each participant one to two days before each scheduled session and if

requested the morning of their appointment. During these calls/texts participants were reminded of the date and time of their session, as well as requirements for participation.

Demographic Summary

A total of 282 community volunteers were contacted either by phone, text, or email who met the initial screening criteria for the study and were invited to continue their participation either by scheduling an in-person screening appointment or re-screening online or via a phone interview to update their current health status and tobacco use if they were contacted from the registry (required for participants whose previous screening interview was more than one month out of date). Of the 282 individuals contacted, only 35 volunteers came into the lab for the second, in-person screening interview. Out of the 35 individuals that provided informed consent, 13 were not eligible, and eight did not complete the study. Of the eight participants that did not complete the study, four were discontinued due to the COVID-19 shut down, one was discontinued for failure to attend study sessions, one was discontinued for lack of venous access, and two were discontinued due to failure to comply with study requirements. Of the 13 that were ineligible to participate, three were ineligible due to self-reported current health or psychiatric conditions/diseases, three were ineligible due to sustained high blood pressure, one was ineligible due to being < 110 pounds, two were ineligible due to having smoked cigarettes < 1 year, one was ineligible due to cannabis use > 15 days/month, one was ineligible due to past month illicit drug use, one was ineligible due to past-30 day ECIG use, and one was ineligible due to other tobacco use prior to the change in eligibility requirements regarding other tobacco use. Recruitment challenges and the COVID-19 shutdown resulted in a smaller sample size than the target sample size calculated from the a-priori power analysis. Only participants that completed all study sessions were included in the final analyses.

A total of 14 participants completed all five study sessions and were included in analyses. As indicated by Table 2, participants in this study included nine men and five women that were on average (SD) 37.1 years (10.5) of age. Seven participants self-identified as Black or African-American, six as White or Caucasian, and one as more than one race. Thirteen participants self-identified as non-Hispanic or Latino, and one participant identified as Hispanic or Latino. Participants who completed the study smoked on average 14.2 cigarettes (4.4) per day for a mean duration of 11.4 years (9.9), and self-reported smoking for a total of 16.7 years (9.4). Participants' mean expired CO concentration during the in-person screening session was 22.1 ppm (13.7), consistent with participants' self-reported current cigarette smoking status. Furthermore, participants' mean score of 5.1 (1.7) on the Fagerström Test for Cigarette Dependence (scores range from mild dependence [< 4 points], to moderate dependence [4-6 points], and high dependence [7-10 points]; Fagerström, 2011; Heatherton et al., 1991) and participants' mean score of 12.9 (2.2) on the Penn State Cigarette Dependence Index (score range from not dependent [< 4 points], low dependence [4-8 points], medium dependence [9-12 points], and high dependence [13-20 points]; Foulds et al., 2015) suggest that this sample had a moderate to high level of cigarette/nicotine dependence. Nine of the participants had made at least one quit attempt in their lifetime. Only three participants reported using other tobacco products besides tobacco cigarettes (i.e., little cigars and/or cigarillos) after removing other tobacco product use (besides ECIGs) as an exclusion criterion. Six participants reported a preference for menthol-flavored tobacco cigarettes and eight reported a preference for non-menthol tobacco cigarettes.

Table 2.

Overall Demographic and Screening Data for Study Completers (N=14)

	Mean or N	**SD or %**
Age (years)	37.07	10.5
Female	5	35.7%
Male	9	64.3%
Hispanic or Latino	1	7.1%
Non-Hispanic or Latino	13	92.9%
Black or African American	7	50.0%
White or Caucasian	6	42.9%
More than one race	1	7.1%
Cigarettes/day	14.21	4.4
Years Smoking Above Number of Cigarettes	11.43	9.9
Years Smoking Total	16.71	9.4
Fagerström TND [a]	5.14	1.7
Penn State Dependence [b]	12.93	2.2
Menthol Smokers	6	42.9%
Quit Attempts (yes)	9	64.3%
Other Tobacco Product Use (yes)	3	21.4%
Past Month Cannabis Use (yes)	4	28.6%
Cannabis Use (days/month) [c]	4.75	6.2
Past Month Alcohol Use (yes)	11	78.6%
Alcohol Use (days/month) [d]	4.18	4.5
Drinks in a Typical Day	1.36	1.9
Education (years)	13.79	1.8
Unemployed	9	64.3%
Part-time employed	3	21.4%
Full-time employed	1	7.1%
Student	1	7.1%

[a] The Fagerström Test for Cigarette Dependence (Fagerström, 2011).

[b] Penn State Cigarette Dependence Index (Foulds et al., 2015)

[c] Data from four participants who reported smoking cannabis.

[d] Data from 11 participants who reported drinking alcohol.

Materials

During each of the five sessions, participants were provided with one of five study products; a 30 W, KangerTech Subtank Mini ECIG, with a 0.5 Ω CLOCC coil filled with one of four ECIG liquid solutions or OB (participants preferred brand and flavor of cigarettes purchased and provided by CSTP). The four liquids were unflavored, 30/70 PG/VG ratio and only differed by the presence of the sweetener sucralose (0 or 2 mg/mL) or the presence of protonated nicotine (0 or 15 mg/mL nicotine concentration). Thus, the four ECIG liquid solutions were either, 1) sucralose-sweetened and contained 15 mg/mL nicotine concentration ECIG liquid solution (S_15), 2) sucralose-sweetened and contained 0 mg/mL ECIG liquid solution (S_0), 3) unsweetened and contained 15 mg/mL nicotine-containing ECIG liquid solution (U_15), or 4) unsweetened and contained 0 mg/mL nicotine ECIG liquid solution (U_0). All ECIG liquid solutions were made by and purchased from a single ECIG vendor (AVAIL, Richmond, VA). The sucralose concentration that was chosen for this study was intended to be representative of the average sucralose levels in the ECIG liquid solutions produced by the manufacturer. Liquid nicotine concentration was verified independently by VCU's Bioanalytical Shared Resources Laboratory. Coils resistance was verified prior to study sessions via a multimeter and coils were included if their resistance < 1.0 Ω.

Procedure

Once screening was complete, eligible participants were scheduled for five separate lab sessions. Each session was separated by a minimum of 48 hours and occurred no more than twice per week. Each of the five sessions was approximately 3.5 hours long, Latin-square ordered and only differed by tobacco product used during the session. All sessions took place in VCU's CSTP clinical laboratory, where participants completed sessions in separate session

rooms. Participants were required to come into the lab at least 12 hours abstinent from all nicotine and tobacco products, and were asked to provide an expired air CO sample at the beginning of each session to verify abstinence from combustible tobacco (≤ 10 ppm or 50% of their screening CO concentration; BreathCO monitor, Vitalograph, Lenexa, KS). If participants did not meet this requirement, sessions were rescheduled and participants were reminded of study participation requirements. Once a participant's expired air CO was measured and they were deemed compliant with the abstinence restriction, heart rate and blood pressure were measured to determine if participants' blood pressure and heart rate were within the study's safety parameters. If so, participants continued their one-hour rest period prior to the start of the study session. This one-hour rest period has been used in a previous studies to ensure at least one-hour researcher-monitored abstinence of all nicotine and tobacco products (see Hiler et al., 2020; Spindle et al., 2018).

During the one-hour rest period, CSTP staff prepared the session product according to a Latin-square condition order. In each session, participants used one of the five study products. All sessions, except the session that participants used OB, were double-blinded to minimize risks of expectancy bias. Blinding was accomplished by having an unblinded CSTP staff member who did not interact with participants fill four identical opaque bottles with one of the four different ECIG liquids corresponding with the Latin-square ordered session key and assigning them each bottle a different code: 1, 2, 3, 4 or 5 based on session order. These bottles were placed into a bag together and assigned to a participant upon enrolling in the study.

During the rest period, two ECIG devices were prepared and filled with the corresponding ECIG liquid in the assigned bottle for the session number. An extra device was always prepared so that the session could continue if the first device failed. ECIG tanks were

wrapped with opaque tape to keep participants and study administration staff blind to the ECIG liquid color. The session specific ECIG liquid was applied to the cotton wick in the coil and squeezed into the tank and the ECIG devices were left to sit for at least 20 minutes prior to use to allow the ECIG liquid to saturate the device components.

Following the one-hour rest period, participants were connected to the physiological monitoring equipment again to obtain a baseline measure of heart rate and blood pressure. Following this baseline assessment, the blood pressure cuff was removed, but the pulse oximeter remained so that heart rate could be monitored for physiological effects of nicotine during the 10-puff, directed bout and continuously throughout the rest of the session for safety. Participants completed baseline subjective questionnaires and then a nurse collected a baseline blood sample (~ 7.0 mL) from participants' forearm via a butterfly needle. Participants then completed a five-minute, 10-puff, "directed" ECIG/cigarette bout (30 seconds between each puff) that was recorded via puffing topography equipment (as in Hiler et al., 2017; Hiler et al., 2020; Spindle et al., 2017; and Spindle et al., 2018). Immediately following the 10-puff, directed bout, blood was sampled again (~7.0 ml) and participants completed a post-bout battery of subjective questionnaires.

Approximately 25 minutes later, participants completed a modified version of the CPT (as in Barnes et al., 2017; described in further detail below in the materials section) and a cross-price CPT during ECIG sessions. Following the CPTs and an hour after the first blood sample, participants completed subjective effects questionnaires. An hour and ten minutes following the completion of the first product bout, participants completed a 30-minute PRT. Following the PRT, participants completed a fourth and final battery of subjective questionnaires. There was a half-hour waiting period after the PRT ended in an effort to prevent smoking immediately

following the task when participants were dismissed from the session. Therefore, after a 30-minute final waiting period, participants were compensated for their time (initially $100/session for a total of $500 for n = 9; increased to $125/session for a total of $625 for n = 5) and reminded of study restrictions and their upcoming sessions. See Table 2 for the session timeline.

Table 3.

Study Session Timeline.

Time	Session Activity
00:00	Participant arrives, 1-hour acclimation period begins (CO test).
00:55	Attach physiological equipment.
01:00	Baseline subjective effects questionnaires: HH[1], DEN[2], QSU[3], PANAS[4]
01:10	Baseline blood sample.
01:15	Five-minute, 10-puff, directed ECIG/cigarette bout.
01:20	Second blood sample (immediately after last puff), subjective effects questionnaires: HH, QSU, DEN, PANAS, GLMS[5], LHS[6], DEQ[7], CEQ[8], WUA[9].
01:45	CPT[10] and CP-CPT[11]
02:20	Subjective effects questionnaires: HH, QSU, PANAS.
02:30	PRT[12]
03:00	Subjective effects questionnaires: HH, QSU, PANAS.
03:30	Participants disconnected from physiological equipment, compensated, and released.

Note. Abbreviations in order of appearance: [1]HH = Hughes and Hatsukami Tobacco Withdrawal Scale, [2]DEN = Direct Effects of Nicotine Scale, [3]QSU = Questionnaire of Smoking Urges-brief, [4]PANAS = Positive and Negative Affect Schedule, [5]GLMS = General Labeled Magnitude Scale, [6]LHS = Labeled Hedonic Scale, [7]DEQ = Drug Effects Questionnaire, [8]CEQ = Cigarette Evaluation Questionnaire, [9]WUA = Willingness to use again question, [10]CPT = Cigarette Purchase Task, [11]CP-CPT = Cross-Price Cigarette Purchase Task, and [12]PRT = Progressive-Ratio Task.

Participant Safety and Rights

CSTP staff were trained to ensure that participant safety and rights were maintained throughout the entire duration of the study. During the consent process participants were told that some of the ECIG devices they would be using during the study would contain nicotine and that others would not, but an exact nicotine amount or schedule of administration was not provided to participants and device settings were kept concealed to protect the integrity of the study and to minimize the risk of expectancy bias (Griffiths et al., 2003; Carter & Griffiths, 2009). Participants were made aware that they could experience some discomfort prior to sessions when they were required to abstain from all nicotine and tobacco products for 12 hours. The side effects of nicotine/tobacco abstinence can include irritability, anxiety, restlessness, excessive hunger, difficulty concentrating, and/or sleep disturbance. While these side effects may have been uncomfortable to participants, they did not impose any medical danger or threat to participants' health or safety. During study sessions, participants were asked to use one of four ECIG device/liquid combinations or their usual brand of tobacco cigarette and were made aware that using novel tobacco products could be uncomfortable and could cause side effects such as nervousness, dizziness, nausea, lightheadedness and/or excessive sweating. No serious side effects were reported. The laboratory's trained nurse minimized risks and discomfort during blood sampling by using sterile, disposable equipment. Participants' heart rate was monitored throughout each session for safety purposes. Sessions were stopped if systolic blood pressure dropped below 90 or elevated above 140, diastolic blood pressure dropped below 60 or elevated above 90, and/or if the participant's heart rate dropped below 50 or elevated above 120 bpm for sustained a period of time. No unanticipated adverse events occurred in this study.

Potentially identifiable information that was collected about participants included their name and signature on the consent form, birthdate, and basic demographic information collected on the screening forms. Consent forms were stored separately from research data. All paper and computer-based research data were identified by an alphanumeric code and stored in locked cabinets in locked rooms only accessible by CSTP staff. All computers were password protected. If at any time a participant found the data collection procedures unacceptable, they were able to discontinue their participation without any penalty and were able to keep all compensation earned up until that point. Participation was stopped by study staff without consent for reasons that included study requirement noncompliance, failure to attend sessions, or the study staff believed that withdrawal from the study was necessary for the participant's health or safety.

Outcome Measures

Plasma Nicotine

Blood samples were collected two times during each session, immediately before and after a five-minute, 10-puff, directed product bout to assess nicotine delivery of the study products. Blood samples were only collected at these two time points to minimize unnecessary participant burden, as data after the PRT are non-systematic due to the variable number of puffs earned on the PRT. Immediately after blood collection, samples were centrifuged, and serum was collected and stored at -70° C. Blood samples were sent to VCU's Department of Pharmaceutics Bioanalytical Analysis Core Laboratories for blood nicotine concentration analyses (see Breland et al., 2006). The limit of quantitation (LOQ) for nicotine concentration was 2.00 ng/mL, thus values below 2.00 ng/mL were replaced with 2.00 ng/mL to provide a conservative estimate of nicotine delivery (Vansickel et al., 2010).

Heart Rate

A Criticare Systems model 507 monitored heart rate (every 20 seconds) continuously. Heart rate data was used to determine if nicotine-containing products delivered physiologically active amounts of nicotine to users.

Puff Topography

Puff topography was measured during the 10-puff, directed bout. Puff topography instruments were developed and manufactured at American University of Beirut (AUB; see Hiler et al., 2017; Spindle et al., 2017; Spindle et al., 2018) and measured five puff topography variables: puff duration, puff volume, puff number, inter-puff interval, and flow rate. The measurement apparatus required that the ECIG and/or cigarette be placed in a mouthpiece that detected flow-induced pressure changes across an orifice as a result of inhalation. The pressure changes were sensed by a pressure transducer and converted to flow rate (puff velocity) via previously calibrated software. The converted flow rate measurements were subsequently used by the software to calculate the other puff topography variables (Blank et al., 2009). Importantly, the device provided sensitivity sufficient to ensure valid measurements at puff velocities as low as 3 mL/sec to measure the low flow rates (i.e., puff velocities) observed with ECIG use accurately (Spindle et al., 2017). Multiple mouthpieces were made for the ECIG device used in the current study. Each mouthpiece was cleaned and the mouthpiece and topography measurement device calibrated with an automatic digital flow calibrator prior to each session.

Cigarette Purchase Task (CPT)

A modified version of the Cigarette Purchase Task (CPT; similar to Barnes et a., 2017; Jacobs & Bickel, 1999; MacKillop et al., 2008), was used to estimate the demand and assess the reinforcement efficacy of the study products. Participants completed the CPT approximately 25

minutes after the 10-puff, directed bout. The CPT asked participants to imagine a typical day during which they smoked and didn't have access to any tobacco products besides the session product, and report how many times they would take 10 puffs from the session product at varying prices. Prices included: $0 (free), $0.01, $0.02, $0.05, $0.10, $0.25, $0.50, $0.75, $1.00, $1.50, $2.00, $3.00, $4.00, $5.00, $7.00, $10.00, $15.00, and $20.00 (See appendix B). The CPT had five outcome measures: demand intensity (i.e., the amount of hypothetical consumption when the product is free), demand elasticity (i.e., the change/sensitivity in consumption of a product as a function of the change in price), breakpoint (i.e., the corresponding product price when consumption ceases), Omax (i.e., the most amount of money spent on the product), and Pmax (i.e., the corresponding price of the maximum expenditure on the product).

Cross-Price Cigarette Purchase Task (CP-CPT)

A cross-price cigarette purchase task (CP-CPT) was used to measure how many 10-ECIG puff uses participants would purchase per day if the ECIG puffs were concurrently available at a constant price ($1.00) while OB increased in price (same prices as the above CPT; see appendix C). Participants completed the CP-CPT immediately following the single product CPT in all sessions except OB, during which they only received the single-product CPT. The CP-CPT produced the outcome measure cross-price elasticity that was used to estimate if the ECIG conditions could be used for cigarette substitution (similar to Grace et al., 2014; O'Conner et al., 2014).

Progressive-Ratio Task

The PRT (similar to Copp et al., 2015) was administered one hour and ten minutes after participants had the chance to sample the product during the directed, five-minute, 10-puff. The PRT was a 30-minute computerized task where participants had the option to earn puffs during

this time by pressing the spacebar. The first puff required ten key presses, and after each reinforcer (puff) was earned and consumed the work requirement to earn the subsequent puff increased by 30% (i.e., 10, 13, 17, etc.; as in Barrett, 2010; 2011; Copp et al., 2015). Participants were signaled with a brief feedback tone for a successful response. The PRT had three outcome measures: 1) breakpoint (maximum number of key presses completed to earn a puff), 2) number of puffs, and 3) latency (sec) to initiate key pressing.

Subjective Effects Questionnaires

A total of nine subjective effects questionnaires were administered during each session. The Hughes and Hatsukami Tobacco Withdrawal Scale (HH), the Tiffany-Drobes Questionnaire of Smoking Urges-brief (QSU), and the Positive and Negative Affect Schedule (PANAS) were administered a total of four times, before and after the 10-puff, directed bout, and before and after the PRT. The Direct Effects of Nicotine (DEN) scale was administered twice, before and after the 10-puff, directed bout. The Cigarette Evaluation Questionnaire (CEQ), Drug Effects Questionnaire (DEQ), the general Labeled Magnitude Scale (GLMS), Labeled Hedonic Scale (LHS) and questions about willingness to use the product again were administered once, immediately following the 10-puff, directed bout. All questionnaires were administered via a computer using the survey system REDCap. A detailed description of each subjective questionnaire is below.

Hughes and Hatsukami Tobacco Withdrawal Scale (HH). An adapted version of the Hughes and Hatsukami Tobacco Withdrawal scale was used to measure the suppression of nicotine/tobacco abstinence symptoms (Hughes & Hatsukami, 1986). This shortened version of the scale consisted of eleven items; “Anxious”, “Craving a cigarette/nicotine”, “Depression/feeling blue”, “Difficulty concentrating”, “Drowsiness”, “Hunger”, “Impatient”,

"Irritability/frustration/anger", "Restlessness", "Desire for sweets", and "Urges to smoke" (See appendix D). The items "Insomnia/disturbed sleep" and "Increased eating" were excluded from the shortened version of the scale, as these items were not relevant during the sessions. Responses were recorded via a computerized visual analog scale where participants were asked to click on a horizontal line from "not at all" to "extremely" and scores (0-100) were expressed as a percentage of total line length. Each item was scored individually.

Tiffany-Drobes Questionnaire of Smoking Urges-Brief (QSU). The QSU-brief (Cox, Tiffany, & Christen, 2001) was used to measure nicotine abstinence. The QSU-brief consisted of ten smoking-related items: "I have a desire for a cigarette right now", "Nothing would be better than smoking a cigarette right now", "If it were possible, I probably would smoke right now", "I could control things better right now if I could smoke", "All I want right now is a cigarette", "I have an urge for a cigarette", "A cigarette would taste good now", "I would do almost anything for a cigarette now", "Smoking would make me less depressed", and "I am going to smoke as soon as possible" (See appendix E). Responses were recorded via a discrete choice scale ranging from 1 (not at all) to 7 (extremely). Items were scored into two aspects of craving; a desire and intention to smoke (Factor 1) and anticipation of relief from smoking abstinence (Factor 2).

Positive and Negative Affect Schedule (PANAS). The PANAS scale was used to measure changes in participant mood (Watson, Clark, & Tellegen, 1988). This scale consisted of 20 items: "interested", "distressed", "excited", "upset", "strong", "guilty", "scared", "hostile", "enthusiastic", "proud", "irritable", "alert", "ashamed", "inspired", "nervous", "determined", "attentive", "jittery", "active", and "afraid" (See appendix F). Responses were recorded with a scale ranging from 0 (very slightly or not at all) to 5 (extremely). The 20 items were grouped into two subscales, positive affect and negative affect.

Cigarette Evaluation Questionnaire (CEQ). A modified version of the Cigarette Evaluation Questionnaire (CEQ) was used to assess the reinforcing effects and adverse effects of product use (Cappelleri et al., 2007). The CEQ consisted of 12 items that have been modified to represent smoking and ECIG use (i.e., product use); “Was the product satisfying?”, “Did the product taste good?”, Did you enjoy the sensations in your throat and chest?”, “Did using the product calm you down?”, “Did using the product make you feel more awake?”, “Did using the product make you feel less irritable?”, “Did using the product help you concentrate?”, “Did using the product reduce your hunger for food?”, “Did using the product make you dizzy?”, “Did using the product make you nauseous?”, “Did using the product immediately relieve your craving for a cigarette?”, and “Did you enjoy using the product?” (See appendix G). Responses were recorded on a seven-point scale ranging from 1 for "Not at all" to 7 for "Extremely." Items were scored and analyzed individually.

Drug Effects Questionnaire (DEQ). The Drug Effects Questionnaire (DEQ) was modified to assess the strength of drug effects and desirability of drug effects (de Wit & Phillips, 2012). The DEQ consisted of five items: “Do you feel a drug effect right now?”, “Do you like any of the effects [that] you are feeling right now?”, “Do you dislike any of the effects [that] you are feeling right now?”, “Do you have a rush/buzz right now?”, and “Would you like more of the product you used, right now?” (See appendix H). Responses were recorded via a computerized visual analog scale where participants clicked on a horizontal line from “not at all” to “extremely” and scores (0-100) were expressed as a percentage of total line length. Each item was scored individually.

Direct Effects of Nicotine (DEN) scale. The Direct Effects of Nicotine (DEN) scale was used to measure the effects of nicotine/product use. This DEN was modified from a previous

study (Perkins et al., 1994) and consisted of ten items: “Nauseous”, “Dizzy”, “Lightheaded”, “Nervous”, “Sweaty”, “Headache”, “Excessive salivation”, “Heart-pounding”, “Confused”, and “Weak” (Evans et al., 2006; see appendix I). Responses were recorded via a computerized visual analog scale where participants clicked on a horizontal line from “not at all” to “extremely” and scores (0-100) were expressed as a percentage of total line length. Each item was scored individually.

General Labeled Magnitude Scale (GLMS). The general Labeled Magnitude Scale (Green et al., 1993) was used to measure product sensations. This scale will be modified to measure three items: “How would you describe the overall sweetness of the product you just used?”, “How would describe the overall harshness/irritancy of the product you just used?”, and “How would you describe the overall throat hit of the product you just used?” (See appendix J). Responses were recorded via a computerized visual analog scale where participants clicked on a vertical line from “no detectable sensation” anchored at the bottom to “the strongest imaginable sensation of any kind” (0-100) anchored at the top, with the labels barely detectable, weak, moderate, strong, and very strong spaced quasi-logarithmically from bottom to the top of the scale. Each item was scored individually.

Labeled Hedonic Scale (LHS). The Labeled Hedonic Scale (Lim et al., 2009) was used to measure participants liking of the product sensations measured in the GLMS. The scale was modified to measure three items: “How would you describe the overall sweetness of the product you just used?”, “How you would describe the overall harshness/irritancy of the product you just used?”, and “How would you describe the overall throat hit of the product you just used?” (See appendix K). Responses were recorded via a computerized visual analog scale where participants clicked on a vertical line from “most disliked sensation imaginable” to “most liked sensation

imaginable" (0-100) and scores were expressed as a percentage of total line length. Each item was scored individually.

Willingness to Use Again Questions. The perceptions of product use and willingness to use again questions consisted of four questions that assessed participants' willingness to use the product again: "How likely would you be to use this product again if it was offered to you by a close friend?", "How likely would you be to buy this product for personal use?", "How likely would you be to recommend this product to a smoker who is trying to reduce or quit smoking?", and "Do you think there was nicotine in the product you used today?" (See appendix L). Responses to all but the last item were recorded via a computerized visual analog scale where participants clicked on a horizontal line from "Not at all likely" to "Extremely likely" (0-100) and scores were expressed as a percentage of total line length. The last item had two response options 'yes' or 'no'. Each item was scored individually.

Data Analysis Plan

The statistical analyses for the outcome measures were performed using IBM SPSS (Version 27.0) and GraphPad Prism (Version 6). For each outcome variable in the current study, two types of analyses were conducted using single-factor repeated-measures analysis of variance (ANOVA) and repeated-measures ANOVAs. The primary analyses included all five study products to examine differences between the study products in relation to OB cigarettes. The secondary analyses was conducted only on the ECIG conditions in order to better understand and assess the impact of sucralose and nicotine on ECIG abuse liability outcomes. Violations of sphericity were corrected using the Huynh-Feldt correction (Huynh & Feldt, 1976) and post-hoc tests were conducted with Tukey's HSD testing (Tukey, 1949) on any significant interactions or main effects that had three or more condition comparisons.

Physiological Outcome Measures

For plasma nicotine, values less than the assay's LOQ (2 ng/ml) were replaced with a value of 2 ng/mL (as in Vansickel et al., 2010). Baseline plasma nicotine concentration was subtracted from post-bout nicotine concentration to obtain a measure of nicotine "boost" (as in Hiler et al., 2017). Plasma nicotine boost data were analyzed using a primary, single-factor ANOVA with five levels of "condition" (OB, U_0, S_0, U_15, and S_15) to compare the nicotine delivery across all study products. A secondary, repeated-measures ANOVA was used to compare nicotine boost profiles of the ECIG conditions using a two (nicotine) X two (sucralose) ANOVA.

Heart rate data were averaged across time to produce a single value for baseline and a single value for the five minutes during the 10-puff, directed bout to examine if the products delivered physiologically active nicotine doses. Repeated-measures ANOVAs were used to examine heart rate, specifically, a primary, five (condition) X two (time) ANOVA was conducted to compare the effects of all the study products, and a secondary, two (nicotine) X two (sucralose) X two (time) ANOVA was conducted to compare the effects the ECIG conditions on heart rate.

Behavioral Outcome Measures

The CPT data were prepared similar to previous work (Barnes et al., 2017; Koffarnus et al., 2015; Stein et al., 2015). The CPT data were examined for the presence of demand functions that were not affected by price, referred to as nonsystematic data. Nonsystematic data were identified via three criterion algorithms: trend (i.e., all else being equal increases in price should result in consumption reduction), bounce (i.e., number of "jumps" in consumption that exceed 25% of the initial consumption at the lowest price), and reversals from zero (i.e., consumption

ceases at a given price and then consumption resumes at higher prices; Stein et al., 2015). Outcome measures were compared across study products individually. Cross-price elasticity, or the degree of change in consumption for the ECIG condition when price for OB is increased and the price of the ECIGs stayed the same, was calculated for individual participants as the regression slopes of (log) ECIG demand on (log) cigarette price similar to prior work (i.e., Bono et al., 2020; Stein et al., 2018). A positive cross-price elasticity value would indicate that the ECIG could be used for cigarette substitution (i.e., ECIG consumption increases as a function of price increase), a negative cross-price elasticity value would indicate that the ECIG is a complement to the preferred product (i.e., ECIG consumption decreases as a function of price increase), and a constant or flat relationship slope would indicate that the ECIG is independent of the demand for OB (O'Conner et al., 2014).

The PRT data were prepared similar to previous work (Barrett, 2010; Copp et al. 2015). Raw data for the PRT outcomes breakpoint and latency were log-transformed due to the logarithmic scale of work (30% increase) and the tendency for time measured in milliseconds to be skewed during a 30-minute task (Barrett, 2010; Copp et al. 2015). Kolmogorov-Smimov tests indicated that the normality assumptions were better met for breakpoint and latency following logarithmic transformations. After cleaning the data, single-factor (condition), repeated-measures ANOVAs were conducted with all five study conditions on the CPT variables (breakpoint, demand intensity, Omax, Pmax, demand elasticity) and PRT variables (breakpoint, number of puffs, and latency) to compare the results between all of the study products. Secondary, two (nicotine) X two (sucralose) repeated-measures ANOVAs were used to examine differences among the ECIG conditions.

Primary, single-factor (condition) repeated-measures ANOVAs were conducted with all five study conditions on the puff topography variables (puff number, IPI, puff volume, puff duration, and flow rate) to compare the results between all of the study products. Secondary, two (nicotine) X two (sucralose) repeated-measures ANOVAs were used to examine differences among the ECIG conditions.

Subjective Effects Measures

Repeated-measures ANOVAs were used to examine items from the HH, QSU, and PANAS. The pre- and post-10-puff, directed bout and the pre- and post-PRT time points were analyzed separately so that the effects of nicotine administration and puff variability during the PRT could be taken into consideration when interpreting changes in nicotine abstinence symptoms and mood. Primary analyses were conducted with five (condition) X two (time) ANOVAs to examine changes in mood and nicotine and tobacco abstinence symptoms between all five study conditions. Secondary, two (nicotine) X two (sucralose) X two (time) ANOVAs were conducted on HH, QSU, and PANAS items to compare the impacts of sucralose and nicotine on tobacco abstinence symptom suppression and mood. Repeated-measures ANOVAs were used to examine DEN items. Primary analyses were conducted with five (condition) X two (time) ANOVAs to examine changes in subjective effects between all five of the study conditions. Secondary, two (nicotine) X two (sucralose) X two (time) ANOVAs were also conducted to compare the impacts of sucralose and nicotine between the ECIG conditions on DEN items. Raw data for the GLMS outcomes were log-transformed similar to previous work (i.e., Pullicin et al., 2020; Kim et al., 2016) due to quasi-logarithmically spaced descriptions from bottom to the top of the scale. Once log-transformed, the subjective items from the GLMS and the items from the CEQ, DEQ, LHS, and WUA were analyzed using primary, single-factor

(condition) repeated-measures ANOVAs to examine differences between the five study conditions, and secondary, two (nicotine) X two (sucralose) repeated-measures ANOVAs were conducted to compare the ECIG conditions on subjective effects.

Results

This within-subjects, clinical lab study examined the individual and combined influence of sucralose and nicotine concentration on various measures of abuse liability. Results of all analyses are discussed in the text. Statistics for the primary, single-factor repeated measure ANOVAs are described in the text. Statistics for the primary analyses that involved five (condition) X two (time) repeated measure ANOVAs are reported in Table 4. Statistics for the secondary analyses that involved two (nicotine) X two (sucralose) repeated-measures ANOVAs, and two (nicotine) X two (sucralose) X two (time) repeated-measures ANOVAs are described in Table 5.

Table 4.

Summary of Primary Analysis ANOVA Results for Outcome Measures with Interactions.

Outcome Measure	Condition			Time			Condition × Time		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
HR[1]	7.18	*<.001*	.36	15.80	*<.01*	.55	6.17	*<.001*	.32
Subjective Measures									
Hughes-Hatsukami[a, 1]									
Anxious									
T1-T2	0.95	*ns*	.07	15.39	*<.01*	.54	0.54	*ns*	.04
T3-T4	2.40	*ns*	.16	1.30	*ns*	.09	0.34	*ns*	.03
Craving									
T1-T2	3.41	*<.05*	.21	25.32	*<.001*	.66	3.64	*<.05*	.22
T3-T4	14.81	*<.001*	.53	17.07	*<.01*	.57	15.59	*<.01*	.55
Depression									
T1-T2	0.97	*ns*	.07	6.87	*<.05*	.35	0.96	*ns*	.07
T3-T4	1.23	*ns*	.09	0.58	*ns*	.04	0.42	*ns*	.03
Difficulty concentrating									
T1-T2	0.70	*ns*	.05	20.89	*<.001*	.62	0.59	*ns*	.04
T3-T4	0.81	*ns*	.06	3.09	*ns*	.19	0.15	*ns*	.01
Drowsiness									
T1-T2	0.00	*ns*	.00	23.19	*<.001*	.64	0.98	*ns*	.07
T3-T4	0.55	*ns*	.04	1.16	*ns*	.08	1.06	*ns*	*.08*
Hunger									
T1-T2	0.82	*ns*	.06	17.05	*<.01*	.57	0.44	*ns*	*.03*
T3-T4	1.69	*ns*	.12	4.48	*ns*	.26	0.99	*ns*	.07
Impatient									
T1-T2	1.10	*ns*	.08	10.95	*<.01*	.46	0.26	*ns*	.02
T3-T4	0.76	*ns*	.06	0.03	*ns*	.00	0.28	*ns*	.02
Irritable									
T1-T2	3.10	*<.05*	.19	11.98	*<.01*	.48	1.26	*ns*	.09
T3-T4	2.59	*ns*	.17	0.29	*ns*	.02	0.81	*ns*	.06
Restless									
T1-T2	1.66	*ns*	.11	17.19	*<.01*	.57	0.38	*ns*	.03
T3-T4	2.34	*ns*	.15	0.05	*ns*	.00	0.54	*ns*	.04
Sweets									
T1-T2	1.45	*ns*	.10	3.59	*ns*	.22	0.52	*ns*	.04
T3-T4	1.68	*ns*	.11	3.12	*ns*	.19	0.15	*ns*	.01
Urges to smoke									
T1-T2	4.94	*<.01*	.28	25.41	*<.001*	.66	4.84	*<.01*	.27
T3-T4	14.89	*<.001*	.53	9.32	*<.01*	.42	13.54	*<.01*	.50
Tiffany-Drobes[b, 1]									
Factor 1									
T1-T2	3.30	*<.01*	.20	17.59	*<.01*	.58	4.53	*<.01*	.23
T3-T4	23.67	*<.001*	.65	16.82	*<.01*	.56	16.02	*<.001*	.55
Factor 2									
T1-T2	2.89	*<.05*	.18	11.17	*<.01*	.46	3.41	*<.05*	.21
T3-T4	9.56	*<.001*	.42	1.08	*ns*	.08	5.14	*<.05*	.28
PANAS[c, 1]									
Positive affect									
T1-T2	0.79	*ns*	.06	0.04	*ns*	.00	2.96	*<.05*	.08
T3-T4	0.60	*ns*	.04	6.75	*<.05*	.34	0.17	*ns*	.01
Negative affect									

Outcome Measure	Condition			Time			Condition × Time		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
T1-T2	1.06	*ns*	.08	6.49	*<.05*	.33	2.30	*ns*	.15
T3-T4	1.61	*ns*	.11	0.75	*ns*	.06	0.38	*ns*	.03
Direct Effects of Nicotine[d, 1]									
Confused	0.46	*ns*	.03	2.33	*ns*	.15	0.66	*ns*	.05
Dizzy	3.66	*<.05*	.22	8.24	*<.05*	.39	4.72	*<.05*	.27
Headache	0.69	*ns*	.05	3.29	*ns*	.20	0.72	*ns*	.05
Heart pounding	2.42	*ns*	.16	7.46	*<.05*	.36	0.11	*ns*	.01
Lightheaded	2.66	*ns*	.17	11.56	*<.01*	.47	4.29	*<.01*	.25
Nausea	0.88	*ns*	.06	1.17	*ns*	.08	1.39	*ns*	.10
Nervous	0.79	*ns*	.06	0.49	*ns*	.04	1.05	*ns*	.08
Salivate	3.53	*<.05*	.21	0.89	*ns*	.06	0.28	*ns*	.02
Sweaty	0.31	*ns*	.02	1.68	*ns*	.11	0.39	*ns*	.03
Weak	1.60	*ns*	.11	0.30	*ns*	.02	1.64	*ns*	.11

Note: ns = not significant

[a]HH = Hughes and Hatsukami Tobacco Withdrawal Scale

[b]QSU = Questionnaire of Smoking Urges-brief

[c]PANAS = Positive and Negative Affect Schedule

[d]DEN = Direct Effects of Nicotine Scale

[1]df C = (4, 52); df T = (1, 13); df C x T (4, 52).

Table 5.

Summary of Secondary Analysis (Nicotine by Sucralose Repeated-Measures ANOVA) Results.

	Nicotine			Sucralose			Time			Nicotine × Sucralose			Nicotine × Time			Sucralose × Time			Nicotine × Sucralose × Time		
Outcome Measure	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*P*	η_p^2
Plasma Nicotine Boost[1]	9.14	*<.05*	.43	1.60	*ns*	.12	n/a	n/a	n/a	1.35	*ns*	.10	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HR[2]	11.55	*<.01*	.47	0.90	*ns*	.07	15.26	*<.01*	.54	0.12	*ns*	.01	20.18	*<.001*	.61	0.06	*ns*	.01	1.69	*ns*	.12
Puff Topography[1]																					
Puff number	0.30	*ns*	.02	2.86	*ns*	.18	n/a	n/a	n/a	2.27	*ns*	.15	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
IPI	2.22	*ns*	.15	0.14	*ns*	.01	n/a	n/a	n/a	0.14	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Puff duration	14.15	*<.01*	.52	8.00	*<.05*	.38	n/a	n/a	n/a	0.11	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Puff volume	18.78	*<.01*	.59	5.74	*<.05*	.31	n/a	n/a	n/a	0.09	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Flow rate	2.94	*ns*	.19	0.71	*ns*	.05	n/a	n/a	n/a	0.02	*ns*	.00	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CPT[a, 1]																					
Elasticity	0.13	*ns*	.01	2.72	*ns*	.17	n/a	n/a	n/a	0.13	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Intensity	0.34	*ns*	.03	0.15	*ns*	.01	n/a	n/a	n/a	0.35	*ns*	.03	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Breakpoint	1.21	*ns*	.09	0.12	*ns*	.01	n/a	n/a	n/a	5.19	*<.05*	.29	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Omax	6.72	*<.05*	.34	0.04	*ns*	.00	n/a	n/a	n/a	0.71	*ns*	.05	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pmax	1.83	*ns*	.20	0.20	*ns*	.02	n/a	n/a	n/a	0.69	*ns*	.05	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PRT[b, 1]																					
Breakpoint (log)	0.50	*ns*	.02	0.22	*ns*	.02	n/a	n/a	n/a	9.20	*<.05*	.41	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Puffs	0.55	*ns*	.04	0.23	*ns*	.02	n/a	n/a	n/a	7.45	*<.05*	.36	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Latency (log)	0.02	*ns*	.00	2.88	*ns*	.18	n/a	n/a	n/a	0.79	*ns*	.06	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Subjective Measures																					
Hughes-Hatsukami[c, 2]																					
Anxious																					
T1-T2	2.15	*ns*	.14	1.47	*ns*	.10	14.02	*<.01*	.52	0.43	*ns*	.03	0.63	*ns*	.05	0.32	*ns*	.02	0.24	*ns*	.02
T3-T4	6.88	*<.05*	.35	0.01	*ns*	.00	0.57	*ns*	.04	0.02	*ns*	.00	0.25	*ns*	02	0.41	*ns*	.03	0.26	*ns*	.02
Craving																					
T1-T2	3.74	*ns*	.22	0.00	*ns*	.00	11.28	*<.01*	.47	0.38	*ns*	.03	3.19	*ns*	.20	2.89	*ns*	.18	0.08	*ns*	.01
T3-T4	10.16	*<.01*	.44	0.07	*ns*	.01	1.89	*ns*	.13	0.07	*ns*	.01	0.51	*ns*	.04	0.36	*ns*	.03	0.02	*ns*	.00
Depression																					
T1-T2	1.42	*ns*	.10	0.57	*ns*	.04	6.52	*<.05*	.33	1.22	*ns*	.09	0.71	*ns*	.05	1.79	*ns*	.12	0.24	*ns*	.02
T3-T4	2.03	*ns*	.14	0.68	*ns*	.05	2.03	*ns*	.14	0.92	*ns*	.07	0.02	*ns*	.00	0.67	*ns*	.05	0.01	*ns*	.01
Difficulty concentrating																					
T1-T2	0.45	*ns*	.03	0.97	*ns*	.07	25.71	*<.001*	.66	0.64	*ns*	.05	0.51	*ns*	.04	1.27	*ns*	.01	0.95	*ns*	.07
T3-T4	1.65	*ns*	.11	1.09	*ns*	.08	0.95	*ns*	.07	0.19	*ns*	.01	0.22	*ns*	.02	0.06	*ns*	.00	0.02	*ns*	.00
Drowsiness																					
T1-T2	0.00	*ns*	.00	0.00	*ns*	.00	26.15	*<.001*	.67	0.00	*ns*	.00	2.77	*ns*	.18	0.00	*ns*	.00	0.18	*ns*	.01
T3-T4	1.50	*ns*	.10	0.32	*ns*	.02	2.45	*ns*	.16	0.33	*ns*	.03	0.46	*ns*	.03	0.01	*ns*	.00	1.17	*ns*	.08
Hunger																					
T1-T2	0.08	*ns*	.01	3.64	*ns*	.22	8.39	*<.05*	.39	0.09	*ns*	.01	0.29	*ns*	.02	0.11	*ns*	.01	0.01	*ns*	.00
T3-T4	1.18	*ns*	.08	3.28	*ns*	.20	4.45	*ns*	.26	0.13	*ns*	.01	1.87	*ns*	.13	0.21	*ns*	.02	0.63	*ns*	.05
Impatient																					
T1-T2	3.01	*ns*	.19	3.87	*ns*	.23	9.78	*<.01*	.43	0.79	*ns*	.06	0.10	*ns*	.01	0.01	*ns*	.00	0.01	*ns*	.00
T3-T4	2.01	*ns*	.13	0.13	*ns*	.01	0.35	*ns*	.03	1.02	*ns*	.07	0.38	*ns*	.03	0.08	*ns*	.01	0.10	*ns*	.01
Irritable																					
T1-T2	8.78	*<.05*	.40	0.12	*ns*	.01	8.35	*<.05*	.39	2.12	*ns*	.14	0.47	*ns*	.04	1.27	*ns*	.09	0.96	*ns*	.07
T3-T4	4.66	*ns*	.26	0.55	*ns*	.04	0.00	*ns*	.00	0.03	*ns*	.00	0.15	*ns*	.01	0.01	*ns*	.00	0.87	*ns*	.06
Restless																					
T1-T2	3.35	*ns*	.21	0.63	*ns*	.05	14.04	*<.01*	.52	1.68	*ns*	.11	0.12	*ns*	.01	0.00	*ns*	.00	0.24	*ns*	.02
T3-T4	4.62	*ns*	.26	0.81	*ns*	.06	0.16	*ns*	.01	0.16	*ns*	.01	0.12	*ns*	.01	2.46	*ns*	.16	0.04	*ns*	.00

	Nicotine			Sucralose			Time			Nicotine × Sucralose			Nicotine × Time			Sucralose × Time			Nicotine × Sucralose × Time		
Outcome Measure	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*P*	η_p^2
Sweets																					
T1-T2	0.22	*ns*	.02	0.24	*ns*	.02	1.92	*ns*	.13	3.98	*ns*	.23	3.16	*ns*	.20	1.06	*ns*	.08	0.10	*ns*	.01
T3-T4	1.62	*ns*	.11	1.12	*ns*	.08	2.81	*ns*	.18	1.60	*ns*	.11	0.00	*ns*	.00	0.01	*ns*	.00	0.05	*ns*	.00
Urges to smoke																					
T1-T2	11.38	*<.01*	.47	1.13	*ns*	.01	12.76	*<.01*	.50	0.72	*ns*	.05	3.44	*ns*	.21	1.18	*ns*	.08	1.16	*ns*	.08
T3-T4	6.23	*<.05*	.32	0.04	*ns*	.00	0.70	*ns*	.05	0.00	*ns*	.00	6.60	*<.05*	.34	0.47	*ns*	.04	0.21	*ns*	.02
Tiffany-Drobes[d, 2]																					
Factor 1																					
T1-T2	7.96	*<.01*	.38	0.07	*ns*	.01	10.26	*<.01*	.44	0.25	*ns*	.02	6.03	*<.05*	.31	0.46	*ns*	.03	0.35	*ns*	.03
T3-T4	7.23	*<.05*	.36	1.95	*ns*	.13	0.74	*ns*	.05	0.59	*ns*	.04	3.62	*ns*	.22	2.45	*ns*	.16	0.04	*ns*	.00
Factor 2																					
T1-T2	5.32	*<.05*	.29	0.18	*ns*	.01	9.71	*<.01*	.43	0.79	*ns*	.06	5.14	*<.05*	.28	0.02	*ns*	.00	0.13	*ns*	.01
T3-T4	8.38	*<.05*	.39	0.32	*ns*	.02	0.32	*ns*	.02	0.30	*ns*	.02	1.61	*ns*	.11	0.33	*ns*	.03	0.73	*ns*	.05
PANAS[e, 2]																					
Positive affect																					
T1-T2	1.70	*ns*	.12	1.40	*ns*	.10	1.42	*ns*	.10	0.70	*ns*	.05	0.03	*ns*	.00	6.24	*<.05*	.32	0.18	*ns*	.01
T3-T4	0.00	*ns*	.00	1.50	*ns*	.10	7.13	*<.05*	.35	0.30	*ns*	.02	0.07	*ns*	.01	0.01	*ns*	.00	0.22	*ns*	.02
Negative affect																					
T1-T2	0.00	*ns*	.00	3.51	*ns*	.21	3.48	*ns*	.21	0.01	*ns*	.00	3.28	*ns*	.20	3.54	*ns*	.21	0.00	*ns*	.00
T3-T4	6.31	*<.05*	.33	0.00	*ns*	.00	1.31	*ns*	.09	0.19	*ns*	.01	0.00	*ns*	.00	0.07	*ns*	.01	0.57	*ns*	.04
CEQ[f, 1]																					
Satisfying	2.67	*ns*	.13	7.38	*<.05*	.36	n/a	n/a	n/a	0.74	*ns*	.05	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Taste good	0.04	*ns*	.00	11.42	*<.01*	.47	n/a	n/a	n/a	0.07	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Enjoy throat sensations	0.38	*ns*	.03	1.58	*ns*	.11	n/a	n/a	n/a	0.56	*ns*	.04	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Calm down	3.74	*ns*	.22	1.51	*ns*	.10	n/a	n/a	n/a	2.17	*ns*	.14	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Awake	3.04	*ns*	.19	13.88	*<.01*	.52	n/a	n/a	n/a	5.52	*<.05*	.30	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Less irritable	0.00	*ns*	.00	2.54	*ns*	.16	n/a	n/a	n/a	0.19	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Concentrate	1.41	*ns*	.10	0.92	*ns*	.07	n/a	n/a	n/a	0.06	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Reduce hunger	1.53	*ns*	.11	1.83	*ns*	.12	n/a	n/a	n/a	0.28	*ns*	.02	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dizzy	9.41	*<.01*	.42	1.66	*ns*	.11	n/a	n/a	n/a	0.02	*ns*	.00	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Nauseous	1.21	*ns*	.09	0.19	*ns*	.01	n/a	n/a	n/a	1.00	*ns*	.07	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Craving relief	4.18	*ns*	.24	0.56	*ns*	.04	n/a	n/a	n/a	4.43	*ns*	.25	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Enjoy product	0.28	*ns*	.02	2.15	*ns*	.14	n/a	n/a	n/a	1.75	*ns*	.12	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DEQ[g, 1]																					
Feel	17.64	*<.01*	.58	0.02	*ns*	.00	n/a	n/a	n/a	0.02	*ns*	.00	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Like	2.63	*ns*	.17	0.00	*ns*	.00	n/a	n/a	n/a	0.19	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Dislike	0.57	*ns*	.04	0.00	*ns*	.00	n/a	n/a	n/a	0.20	*ns*	.02	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Buzz	12.02	*<.01*	.48	0.04	*ns*	.00	n/a	n/a	n/a	0.00	*ns*	.00	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
More product	1.18	*ns*	.08	4.67	*<.05*	.26	n/a	n/a	n/a	0.52	*ns*	.04	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Direct Effects of Nicotine[h, 2]																					
Confused	0.67	*ns*	.05	0.06	*ns*	.01	1.57	*ns*	.11	0.17	*ns*	.01	0.62	*ns*	.05	1.25	*ns*	.09	0.06	*ns*	.01
Dizzy	6.51	*<.05*	.33	0.15	*ns*	.01	2.58	*ns*	.17	1.23	*ns*	.09	5.88	*<.05*	.31	0.00	*ns*	.00	0.09	*ns*	.01
Headache	0.01	*ns*	.00	0.37	*ns*	.03	2.93	*ns*	.18	2.31	*ns*	.15	1.68	*ns*	.11	0.02	*ns*	.00	0.33	*ns*	.03
Heart pound	0.17	*ns*	.01	0.78	*ns*	.06	7.62	*<.05*	.37	3.65	*ns*	.22	0.01	*ns*	.00	0.00	*ns*	.00	0.03	*ns*	.00
Lightheaded	3.70	*ns*	.22	0.04	*ns*	.00	3.83	*ns*	.23	3.85	*ns*	.23	1.64	*ns*	.11	0.74	*ns*	.05	1.02	*ns*	.07
Nausea	0.64	*.ns*	.05	1.77	*ns*	.12	1.02	*ns*	.07	0.52	*ns*	.04	3.09	*ns*	.19	0.50	*ns*	.04	0.74	*ns*	.05
Nervous	0.76	*ns*	.06	1.07	*ns*	.08	0.83	*ns*	.06	0.02	*ns*	.00	0.59	*ns*	.04	0.41	*ns*	.03	2.13	*ns*	.14
Salivate	0.15	*ns*	.01	2.17	*ns*	.14	1.07	*ns*	.08	1.64	*ns*	.11	0.04	*ns*	.00	0.64	*ns*	.05	0.43	*ns*	.03
Sweaty	0.02	*ns*	.00	0.06	*ns*	.01	2.30	*ns*	.15	0.77	*ns*	.06	0.26	*ns*	.02	0.52	*ns*	.04	0.42	*ns*	.03
Weak	2.89	*ns*	.18	0.91	*ns*	.07	1.57	*ns*	.11	1.85	*ns*	.13	3.30	*ns*	.20	2.87	*ns*	.18	0.35	*ns*	.03
GLMS[i, 1]																					
Sweetness (log)	6.37	*<.05*	.33	5.08	*<.05*	.28	n/a	n/a	n/a	3.86	*ns*	.23	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Harshness(log)	5.45	*<.05*	.30	0.06	*ns*	.01	n/a	n/a	n/a	0.14	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Throat Hit (log)	14.17	*<.01*	.52	0.22	*ns*	.02	n/a	n/a	n/a	1.02	*ns*	.07	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

	Nicotine			Sucralose			Time			Nicotine × Sucralose			Nicotine × Time			Sucralose × Time			Nicotine × Sucralose × Time		
Outcome Measure	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*P*	η_p^2
LHS[j, 1]																					
Sweetness	0.01	*ns*	.00	0.65	*ns*	.05	n/a	n/a	n/a	1.08	*ns*	.08	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Harshness	1.32	*ns*	.09	0.04	*ns*	.00	n/a	n/a	n/a	0.13	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Throat hit	0.25	*ns*	.02	1.10	*ns*	.08	n/a	n/a	n/a	0.17	*ns*	.01	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
WUA[k, 1]																					
Use again	0.00	*ns*	.00	3.40	*ns*	.21	n/a	n/a	n/a	6.43	*<.05*	.33	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Buy	0.26	*ns*	.02	2.14	*ns*	.14	n/a	n/a	n/a	1.22	*ns*	.09	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Recommend	0.72	*ns*	.05	0.41	*ns*	.03	n/a	n/a	n/a	2.50	*ns*	.16	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Note: ns = not significant, [a]CPT = Cigarette Purchase Task, [b]PRT = Progressive-Ratio Task, [c]HH = Hughes and Hatsukami Tobacco Withdrawal Scale, [d]QSU = Questionnaire of Smoking Urges-brief, [e]PANAS = Positive and Negative Affect Schedule, [f]CEQ = Cigarette Evaluation Questionnaire, [g]DEQ = Drug Effects Questionnaire, [h]DEN = Direct Effects of Nicotine Scale, [i]GLMS = General Labeled Magnitude Scale, [j]LHS = Labeled Hedonic Scale, [k]WUA = Willingness to use again question.

[1]df N = (1, 13); df S = (1, 13); df N x S (1, 13).

[2]df N = (1,13); df S = (1,13); df T = (1,13); df N x S (1, 13); df N x T = (1,13); df S x T = (1,13); df N x S x T = (1,13).

Outcome Measures

Plasma Nicotine Boost

Of the fourteen participants who completed this study, one participant had incomplete blood data and was excluded from the analysis (N=13). Participants with baseline blood nicotine concentrations > 5.0 ng/mL were considered non-abstinent (as in Hiler et al., 2017). One participant was deemed non-nicotine-abstinent (>5.0 ng/mL blood nicotine concentration at baseline) retrospectively after obtaining the blood plasma nicotine concentration results. Despite having high baseline levels (range 13.2 – 31.2 ng/mL), the participant's plasma nicotine concentration remained stable across non-nicotine product use periods and increased after nicotine-containing product use. Data were analyzed with and without the non-abstinent participant included and the overall pattern of results did not differ, thus data from this participant were included in all of the study analyses.

The results from the primary, single-factor (condition) repeated-measures ANOVA for plasma nicotine boost (N =13) revealed a significant effect of condition [F (4, 48) = 14.13, p < .001, η_p^2 = .54]. Post-hoc tests revealed that mean plasma nicotine boost was 12.32 ng/mL (SD = 8.3) in the OB condition, significantly greater than mean nicotine boost in the U_0 condition that was -0.22 ng/mL (1.0) and the S_0 condition that was -0.29 ng/mL (1.1; Tukey's HSD, p < .05), but was not significantly greater than the U_15 condition that was 7.09 ng/mL (8.6) or the S_15 condition that was 5.85 ng/mL (7.0). The mean plasma nicotine boost in the U_15 condition was significantly greater than the U_0 and the S_0 conditions (Tukey's HSD, p < .05; Figure 3). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a main effect of nicotine: collapsed across sucralose conditions, the 15 mg/mL

nicotine-containing ECIG conditions produced a significantly greater mean nicotine boost of 6.47 ng/mL (7.6) compared to when participants used the 0 mg/mL nicotine ECIG conditions that had a mean nicotine boost of -0.25 ng/mL (1.0).

Heart Rate

The results from the primary, five (condition) X two (time) repeated-measures ANOVA for heart rate revealed a significant condition by time interaction. Post-hoc analyses revealed that mean heart rate increased significantly in the OB condition from 73.43 bpm (12.5) at baseline to 80.78 bpm (9.7) during the 10-puff, directed bout. Mean heart rate increased significantly in the U_15 condition from 70.70 bpm (11.6) at baseline to 78.10 bpm (11.8) during the 10-puff, directed bout. Mean heart rate also increased significantly in the S_15 condition from 71.12 bpm (11.3) at baseline to 76.69 (11.0) during the 10-puff, directed bout (Tukey's HSD, $p < .05$). No other significant increases during the 10-puff, directed bout were observed. During the 10-puff, directed bout, mean heart rates in the OB, the U_15, and the S_15 conditions were significantly greater compared to the mean heart rates in the U_0 condition that was 70.91 bpm (11.2) and the S_0 condition that was 70.16 bpm (11.6; Tukey's HSD, $p < .05$; Figure 3). No other significant differences were detected. The results of the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA for heart rate revealed a significant nicotine by time interaction. However, post-hoc test were not able to detect any significant differences between the ECIG conditions.

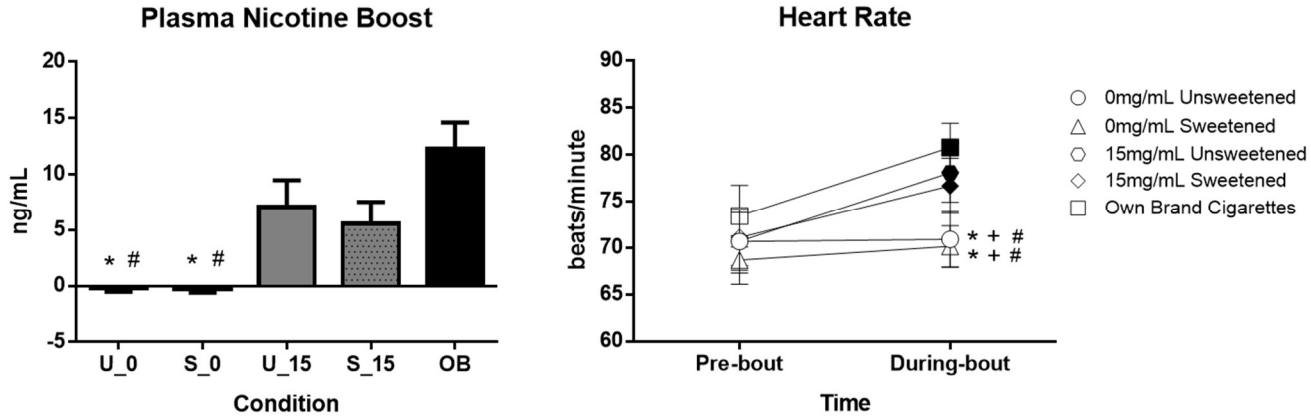

Figure 3. Left panel depicts mean (± SEM) nicotine boost for 13 cigarette smokers. Right panel depicts mean (± SEM) heart rate for 14 cigarette smokers prior to and during the 10-puff directed product bout. Filled symbols in the left panel indicate a significant difference from baseline. Asterisks (*) indicate significant a difference from OB, plus signs (+) indicate a significant difference from S_15, and pound symbols (#) indicate a significant difference U_15 at that time point ($ps < .05$).

Puff Topography

Puff Number. The single-factor (condition) repeated-measures ANOVA for puff number did not detect any significant effects [F (4, 52) = 1.36, $p > .05$, $\eta_p^2 = .10$]; nor did the results from the two (nicotine) by two (sucralose) repeated-measures ANOVA for puff number detect any significant interactions or main effects during the 10-puff, directed bout. Mean puff number for the OB condition was 10.21 (0.8), the U_0 condition was 10.21 (0.6), the S_0 condition was 10.07 (1.1), the U_15 condition was 10.36 (1.4), and the S_15 condition was 9.57 (1.1). This finding was expected due to the research protocol restricting the directed-product bout to ten puffs.

IPI. The single-factor (condition) repeated-measures ANOVA for IPI did not detect any significant effects [F (4, 52) = 0.67, $p > .05$, $\eta_p^2 = .05$]. Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA also did not detect any significant interactions or main effects. Mean IPI for the OB condition was 26.18 (6.9), the U_0 condition was 25.55 (6.9), the S_0 condition was 25.61 (9.6), the U_15 condition was 27.94 (3.1), and the S_15 condition was 26.90 (7.4). This finding was expected due to the research protocol restricting IPI to 30 sec.

Puff Duration. The single-factor (condition) repeated-measures ANOVA for puff duration revealed a significant effect of condition [F (4, 52) = 6.56, $p < .001$, $\eta_p^2 = .34$]. Post-hoc tests revealed that the mean puff duration in the U_15 condition of 1.60 seconds (0.7) was significantly shorter than the U_0 condition's mean of 2.54 seconds (1.8) and the S_0 condition's mean of 2.74 seconds (1.5; Tukey's HSD, $p < .05$), but not the S_15 condition's mean of seconds 1.94 seconds (1.4) or the OB condition's mean of 2.06 seconds (1.3; Figure 4). No other significant differences were observed.

Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA revealed significant main effects of nicotine and sucralose. The main effects analysis for nicotine showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly shorter mean puff duration of 1.77 seconds (1.0) compared to the 0 mg/mL nicotine ECIG condition's mean of 2.64 seconds (0.9). The main effects analysis for sucralose also showed that the sucralose-containing ECIG conditions had a significantly longer mean puff duration 2.34 seconds (1.4) compared to the unsweetened ECIG conditions' mean of 2.07 seconds (1.2).

Puff Volume. The single-factor (condition) repeated-measures ANOVA for puff volume revealed a significant effect of condition [F (4, 52) = 10.82, $p < .001$, $\eta_p^2 = .45$]. Post-hoc tests revealed that the mean puff volume in the OB condition of 65.12 mL (48.3) was significantly smaller than the U_0 condition's mean of 207.17 mL (124.5), the S_0 condition's mean of 233.47 mL (154.7), and the S_15 condition's mean of 166.5 mL (141.0; Tukey's HSD, $p < .05$). The mean puff volume in the S_0 condition was 233.47 mL (154.7), and was significantly larger than the U_15 condition's mean of 130.57 mL (110.4; Tukey's HSD, $p < .05$; Figure 4). No other significant differences were detected.

Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA for puff volume revealed significant main effects of nicotine and sucralose. The main effects analysis for nicotine showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly smaller mean puff volume of 148.54 mL (120.7) compared to the 0 mg/mL nicotine ECIG condition's mean of 220.32 mL (134.6). The main effects analysis for sucralose showed that the sucralose-containing ECIG conditions had a significantly larger mean puff volume of 199.99 mL (142.0) compared to the unsweetened ECIG condition's mean of 168.87 mL (108.6).

Flow Rate (ml/sec). The single-factor (condition) repeated-measures ANOVA for flow rate revealed a significant effect of condition [F (4, 52) = 9.18, $p < .01$, $\eta_p^2 = .41$]. Post-hoc tests revealed that the mean flow rate in the OB condition of 32.21 mL/sec (10.4) was significantly slower than the mean in the U_0 condition of 90.46 mL/sec (58.9), the S_0 condition's mean of 93.33 mL/sec (63.4), and the S_15 condition's mean of 85.00 mL/sec (61.5; Tukey's HSD, $p < .05$), but was not significantly slower than the U_15 condition's mean of 81.07 mL/sec (62.5; Figure 4). No other significant differences were detected. Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

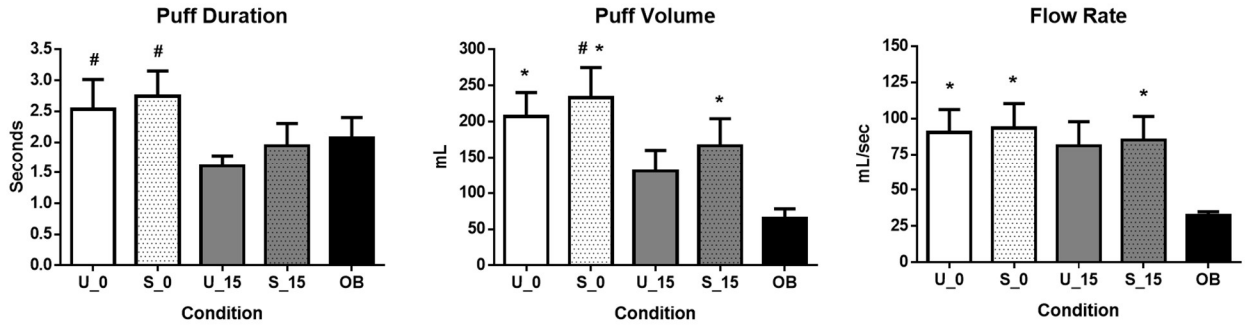

Figure 4. Depicts mean (+SEM) ratings for the topography outcomes puff duration, puff volume, and flow rate during the 10-puff, directed bout for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

Cigarette Purchase Task (CPT)

During the CPT, participants stated how many tobacco cigarettes or number of '10-puff uses' of the ECIG they would hypothetically purchase and smoke/use in a single day at increasing prices and limited to their current budget. The CPT had five outcome measures: demand elasticity (i.e., the change/sensitivity in consumption of a product as a function of the change in price), demand intensity (i.e., the amount of hypothetical consumption when the product is free), breakpoint (i.e., the corresponding product price when consumption ceases), O_{max} (i.e., the most amount of money spent on the product), and P_{max} (i.e., the corresponding price of the maximum expenditure on the product).

Elasticity. Results from the primary, single-factor (condition) repeated-measures ANOVA for elasticity did not detect any significant effects [F (4, 52) = 1.03, $p > .05$, $\eta_p^2 = .07$]. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA also did not detect any significant interactions or main effects for CPT elasticity.

Intensity. Results from the primary, single-factor (condition) repeated-measures ANOVA for intensity revealed a significant effect of condition [F (4, 52) = 5.17, $p < .01$, $\eta_p^2 = .29$]. Post-hoc tests revealed that the mean intensity in the OB condition was 15.29 (4.5), and was significantly greater than the U_0 condition's mean of 8.50 (7.14), the S_0 condition's mean of 9.86 (10.4), the U_15 condition's mean of 8.71 (7.2), and the S_15 condition's mean of 8.36 (7.5; Tukey's HSD, $p < .05$; Figure 5). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Breakpoint. Results from the primary, single-factor (condition) repeated-measures ANOVA for breakpoint did not reveal any significant effects [F (4, 52) = 2.03, $p > .05$, $\eta_p^2 =$

.14]. Although the results from the secondary, two (nicotine) by two (sucralose) revealed a significant nicotine by sucralose interaction, post-hoc tests were not able to detect any significant differences between the ECIG conditions.

O_{max}. Results from the primary, single-factor (condition) repeated-measures ANOVA for O_{max} revealed a significant effect of condition [F (4, 52) = 7.53, $p < .01$, $\eta_p^2 = .37$]. Post-hoc tests revealed that the mean O_{max} in the OB condition was \$6.39 (4.6), and was significantly greater than the U_0 condition's mean of \$2.56 (2.5) and the S_0 condition's mean of \$2.14 (2.0; Tukey's HSD, $p < .05$), but not significantly greater than the U_15 condition's mean of \$2.92 (2.5) or S_15 condition's mean of \$3.54 (3.3; Figure 5). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of nicotine: collapsed across sucralose conditions, the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater O_{max} of \$3.23 (2.3) compared to the 0 mg/mL nicotine ECIG condition's O_{max} that was \$2.35 (2.0).

P_{max}. Results from the primary, single-factor (condition) repeated-measures ANOVA for P_{max} did not reveal any significant effects [F (4, 52) = 0.94, $p > .05$, $\eta_p^2 = .07$]. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA also did not detect any significant interactions or main effects for the CPT outcome P_{max}.

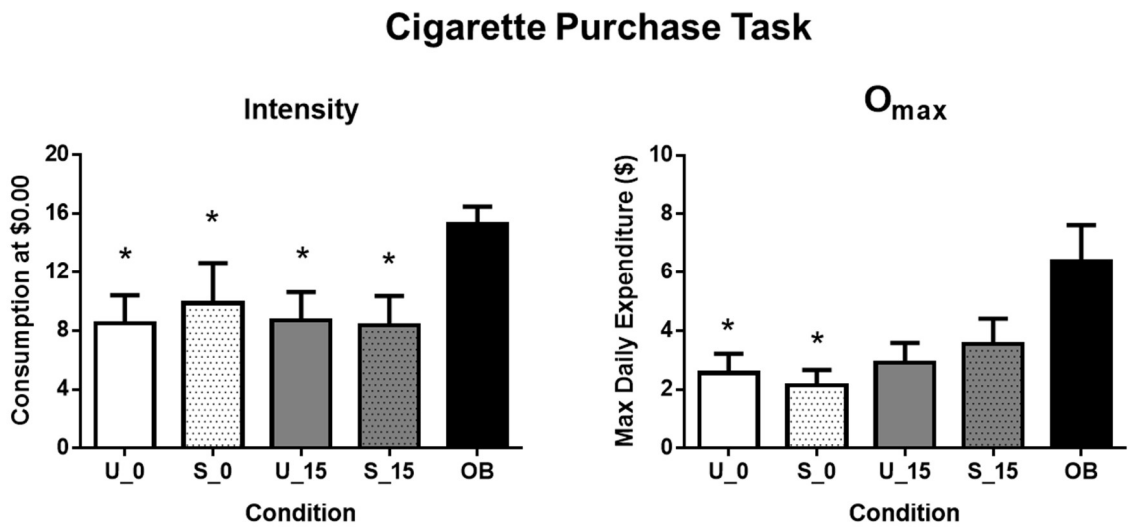

Figure 5. Depicts mean (+SEM) values for the CPT outcomes intensity and O_{max} across all five conditions for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

Cross-Price Cigarette Purchase Task (CP-CPT).

The CP-CPT was used to examine how price increases for the OB condition affect the consumption and substitutability of the ECIG conditions when offered at a constant rate of $1.00 per 10 puffs. Results found that when ECIG puffs cost $1.00 but OB cigarettes were free, 42.9% of participants elected to purchase puffs in the U_0 condition, 42.9% of participants elected to purchase puffs in the S_0 condition, 28.6% of participants elected to purchase puffs in U_15 condition, and 42.9% of participants elected to purchase puffs in the S_15 condition. Linear mixed-effects models indicated that the U_0, the S_0, and the S_15 conditions all had significant negative, cross-price elasticities suggesting that none of the ECIG conditions functioned as a substitution for the OB condition, and instead were found to be weak compliments to the OB condition ($ps < .001$). The cross-price elasticities of the significant ECIG conditions indicated weak relationships between ECIG purchases and OB cigarette price (close to zero; range: - 0.20 to -0.40; see Table 6). The U_15 condition did not have a significant cross-price elasticity (-0.14; $p > .05$) indicating that the demand for the U_15 condition was independent from the demand of OB cigarettes.

Table 6.

Changes in Log-ECIG Consumption Associated with Changes in Log-Price of Own-Brand Cigarettes From the Cross-Price Purchase Task.

ECIG Condition	**Coefficient**	***p***	**95% confidence interval**
Unsweet, 0 mg/mL nicotine	-0.20	*<.001*	[-0.32, -0.08]
Sweetened, 0 mg/mL nicotine	-0.40	<.001	[-0.51, -0.23]
Unsweet, 15 mg/mL nicotine	-0.14	*ns*	[-0.13, 0.10]
Sweetened, 15 mg/ml nicotine	-0.24	*<.001*	[-0.38, -0.10]

Note. Regression coefficients represent a log-ECIG consumption as log price for cigarette increases.

Progressive-Ratio Task (PRT)

The PRT was a 30-minute computerized task during which participants worked to earn puffs from the session product by pressing a space bar on a computer keyboard. The work requirement to earn a puff increased by 30% for each subsequent puff. The PRT had three outcomes: breakpoint (i.e., the maximum number of key presses completed to earn a puff), number of puffs earned, and latency to initiate working for puffs.

Breakpoint. After logarithmically transforming the data, the results from the primary, single-factor (condition) repeated-measures ANOVA for breakpoint revealed a significant effect of condition [F (4, 52) = 4.64, $p < .01$, $\eta_p^2 = .26$]. Post-hoc tests revealed that the mean log breakpoint value for the OB condition was 2.60 (0.5), and was significantly greater than the S_0 condition's mean of 1.62 (1.5) and the U_15 condition's mean of 1.55 (1.3; Tukey's HSD, $p < .05$), but not significantly different from the U_0 condition's mean of 2.14 (1.0), or the S_15 condition's mean of 1.91 (1.3; Figure 6). No other significant differences were detected. Although results from the secondary, two (nicotine) by two (sucralose) ANOVA revealed a significant nicotine by sucralose interaction, post-hoc tests were not able to detect any significant differences between the ECIG conditions.

Puffs Earned. Results from the primary, single-factor (condition) repeated-measures ANOVA for puffs earned during the PRT revealed a significant effect of condition [F (4, 52) = 4.65, $p < .01$, $\eta_p^2 = .26$]. Post-hoc tests revealed that the mean number of puffs earned in the OB condition of 9.93 puffs (4.1) was significantly greater than the mean number of puffs earned in the S_0 condition that was 6.21 puffs (4.7) and in the U_15 condition that was 5.07 puffs (5.1; Tukey's HSD, $p < .05$). Mean puffs in the OB condition did not differ significantly from the mean puffs earned in the U_0 condition that was 7.64 puffs (4.2) or the mean puffs earned in the

S_15 condition that was 7.21 puffs (5.1; Figure 6). No other significant differences were detected. Although the secondary, two (nicotine) by two (sucralose) ANOVA revealed a significant nicotine by sucralose interaction, post-hoc tests were not able to detect any significant differences between the ECIG conditions.

Latency. After logarithmically transforming the data, the results from the primary, single-factor (condition) repeated-measures ANOVA for latency revealed a significant effect of condition [F (4, 52) = 3.10, $p < .05$, $\eta_p^2 = .19$]. Post-hoc tests revealed that participants' latency, or (mean log) time, to respond in the OB condition was significantly shorter than their latency to respond in the U_15 condition (Tukey's HSD, $p < .05$; Figure 6). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

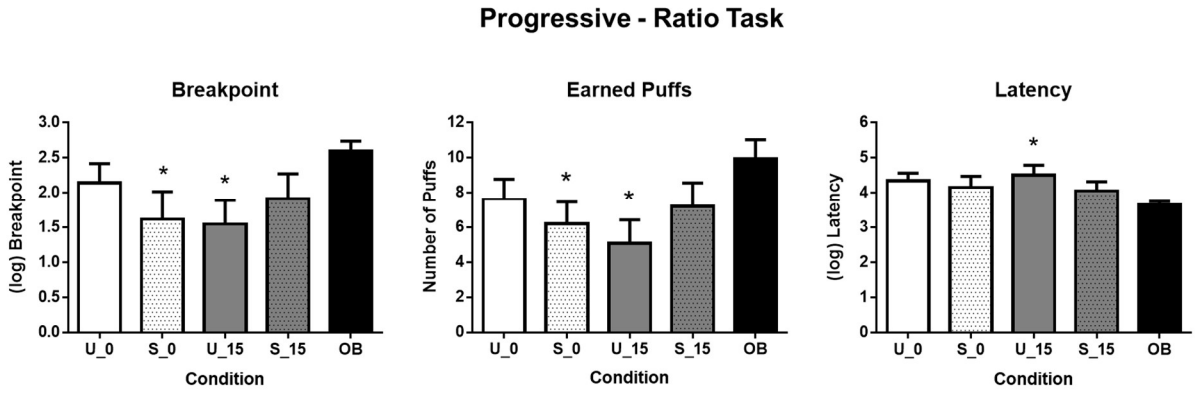

Figure 6. Mean (+ SEM) breakpoint (log transformed), number of puffs, and latency (log transformed) on the PRT for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

Subjective Effects Questionnaires

Hughes and Hatsukami Tobacco Withdrawal Scale (HH).

Anxious. Results from the primary, five (condition) by two (time) repeated-measures ANOVA for the item "Anxious" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. Collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points and a significant main effect of nicotine for the pre- and post- PRT time points. The main effects analysis for time showed that across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. The main effects analysis for nicotine showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean rating for the item "Anxious" of 16.77 (16.5) compared to the 0 mg/mL nicotine ECIG condition's mean rating of 28.13 (25.3) collapsed across the pre- and post-PRT time points. No other significant differences were observed.

Craving a Cigarette/Nicotine. The five (condition) by two (time) repeated-measures ANOVA for the item "Craving a cigarette/nicotine" revealed a significant condition by time interaction for the baseline and post-10-puff, directed bout time points and for the pre- and post-PRT time points. Post-hoc tests revealed that mean craving ratings significantly decreased in the OB condition from 75.21 (28.7) at baseline to 39.71 (22.8) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). Mean craving ratings also significantly decreased in the S_15 condition from 74.57 (25.7) at baseline to 51.93 (31.6) following the 10-puff, directed bout (Tukey's HSD,

$p < .05$). No other significant changes from baseline were observed. Following the 10-puff, directed bout, the mean craving rating in the OB condition was significantly lower than the mean rating of 69.71 (29.7) in the U_0 condition and the mean of 67.00 (28.6) in the S_0 condition (Tukey's HSD, $p < .05$; Figure 7).

Following the PRT, mean craving ratings in the OB condition significantly decreased from 68.79 (21.0) to 19.00 (16.31; Tukey's HSD, $p < .05$). No other significant decreases in craving ratings following the PRT were observed. Following the PRT, the mean craving rating in the OB condition of 19.00 (16.31) was significantly lower than the U_0 condition's mean of 75.00 (22.8), the S_0 condition's mean of 73.00 (23.7), the U_15 condition's mean 60.93 (23.7), and the S_15 condition's mean of 61.21 (21.3; Tukey's HSD, $p < .05$). No other significant differences between conditions were observed.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVAs revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points, and a significant main effect of nicotine for the pre- and post-PRT time points. The main effects analysis for time showed that collapsed across ECIG conditions participants' scores significantly decreased from baseline following the 10-puff, directed bout. The main effects analysis for nicotine showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean rating of 64.63 (16.7) compared to the 0 mg/mL nicotine ECIG condition's mean rating of 76.05 (16.9) collapsed across the pre- and post-PRT time points. No other significant differences were observed.

Depression/Feeling Blue. The five (condition) by two (time) repeated-measures ANOVA for the item "Depression/feeling blue" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. The main effects analysis for time showed

that collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points. Similar to above, collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were observed.

Difficulty Concentrating. The five (condition) by two (time) repeated-measures ANOVA for the item "Difficulty concentrating" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. The main effects analysis for time showed that collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points. Similar to above, collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were observed.

Drowsiness. The five (condition) by two (time) repeated-measures ANOVA for the item "Drowsiness" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. The main effects analysis for time showed that collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the separate, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time

for the baseline and post-10-puff, directed bout time points. Similar to above, the main effects analysis for time showed that collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were observed.

Hunger. The five (condition) by two (time) repeated-measures ANOVA for the item "Hunger" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. The main effects analysis for time showed that collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points. Similar to above, the main effects analysis of time showed that collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected.

Impatient. The five (condition) by two (time) repeated-measures ANOVA for the item "Impatient" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. Collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points. Similar to above, the main effects analysis of time showed that collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were observed.

Irritability/frustration/anger. The five (condition) by two (time) repeated-measures ANOVA for the item "Irritability/frustration/anger" revealed a significant effect of condition and time for the baseline and post-10-puff, directed bout time points. Collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. However, post-hoc tests were not able to detect any significant differences between conditions collapsed across time points. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of nicotine and time for the baseline and post-10-puff, directed bout time points. The main effects analysis for nicotine showed that collapsed across time, the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean rating of 16.93 (18.6) compared to the 0 mg/mL nicotine ECIG condition's mean rating that was 25.91 (27.1). Collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were observed.

Restlessness. The five (condition) by two (time) repeated-measures ANOVA for the item "Restlessness" revealed a significant effect of time for the baseline and post-10-puff, directed bout time points. Collapsed across conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for the baseline and post-10-puff, directed bout time points. Similar to above, collapsed across ECIG conditions, participants' scores significantly decreased from baseline following the 10-puff, directed bout. No other significant differences were observed.

Desire for Sweets. The five (condition) by two (time) repeated-measures ANOVA for the subjective item "Desire for sweets" did not detect any significant interactions or main effects. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Urges to Smoke. The five (condition) by two (time) repeated-measures ANOVAs for the item "Urges to smoke" revealed a significant interaction between condition and time, for the baseline and post-10-puff, directed bout time points and for the pre- and post- PRT time points. Post-hoc tests revealed that mean ratings decreased significantly in the OB condition from 75.36 (24.0) at baseline to 45.86 (21.5) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). Mean rating decreased in the U_15 condition from 70.79 (24.2) at baseline to 55.64 (18.5) following the 10-puff, directed bout, and ratings also decreased in the S_15 condition from 72.50 (26.7) at baseline to 57.36 (22.8) following the 10-puff, directed bout (Tukey's HSD, $p < .05$; Figure 7). No other significant changes from baseline were observed. Following the 10-puff, directed bout, the mean ratings for the OB condition, the U_15 condition, and the S_15 condition were significantly lower than the mean rating in the U_0 condition of 72.86 (16.8; Tukey's HSD, $p < .05$). Following the 10-puff, directed bout, the mean rating in the OB condition was also significantly lower than the mean rating in the S_0 condition of 65.79 (23.4; Tukey's HSD, $p < .05$). Prior to the PRT, participants' mean rating in the OB condition was 64.29 (25.3) and significantly decreased to 25.43 (19.6) following the PRT (Tukey's HSD, $p < .05$). No other significant changes between the pre- and post-PRT time points were observed. The mean rating in the OB condition was significantly lower than the U_0 condition's mean of 76.50 (17.7), the S_0 condition's mean of 72.93 (23.8), the U_15 condition's mean 61.36 (21.6), and the S_15

condition's mean of 60.50 (21.9) following the PRT (Tukey's HSD, $p < .05$). No other significant differences between conditions were observed.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVAs revealed a significant main effect of nicotine and time was observed for the baseline and post-10-puff, directed bout time points, and a significant interaction of nicotine by time for the pre- and post-PRT time points. The main effects analysis for time showed that across ECIG conditions participants' scores significantly decreased from baseline following the 10-puff, directed bout. The main effects analysis for nicotine showed that collapsed across sucralose conditions and the baseline and post-10-puff, directed bout time points, the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean rating of 64.07 (20.5) compared to the 0 mg/mL nicotine ECIG condition's mean rating of 73.13 (18.5). No other significant changes between the pre- and post-PRT time points were observed.

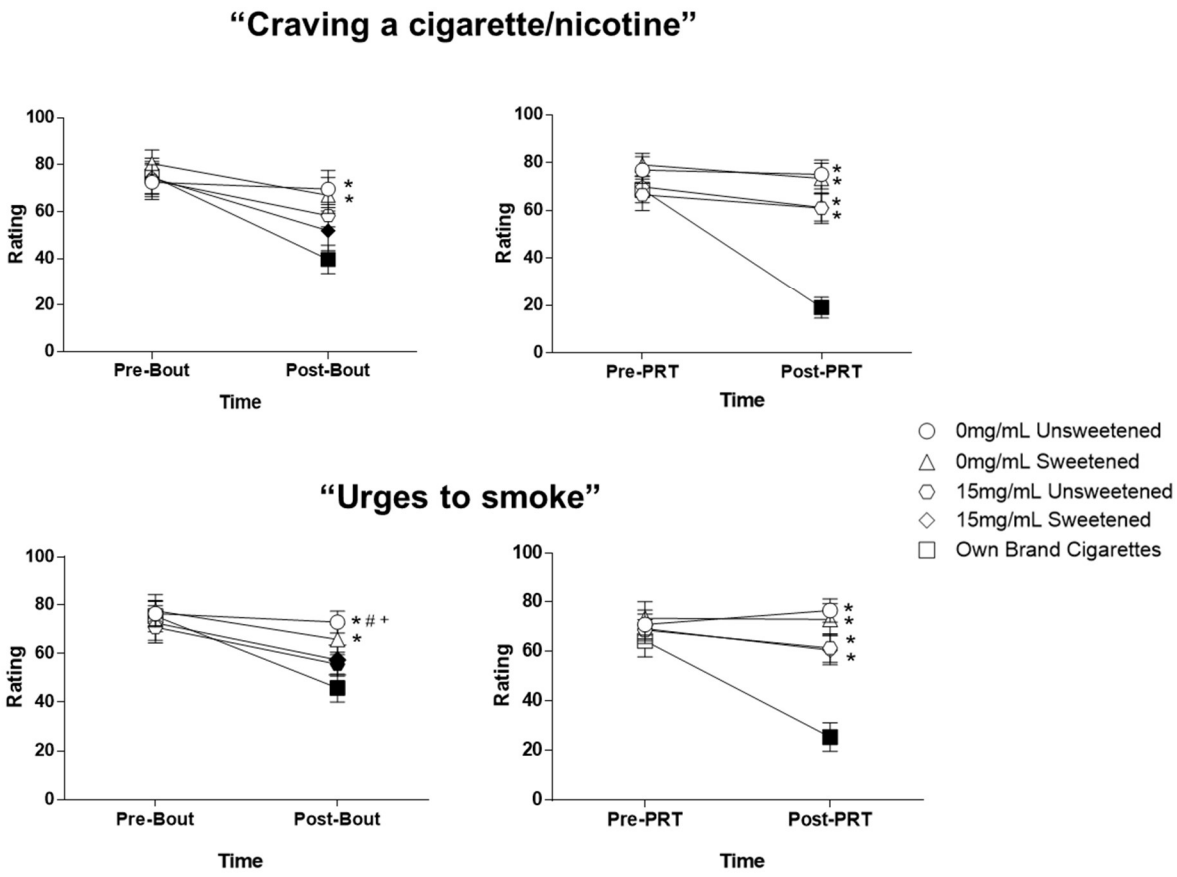

Figure 7. Mean (± SEM) "Craving a cigarette/nicotine" and "Urges to smoke" rating across time for 14 cigarette smokers. Items with the highest *F*-values on the HH item are depicted in the panel. In all other respects, the figure is identical to Figure 3.

Questionnaire of Smoking Urges-Brief (QSU).

Factor 1 (Desire and Intention to Smoke). The five (condition) by two (time) repeated-measures ANOVAs for the Factor 1 score revealed a significant interaction between condition and time for the baseline and post-10-puff, directed bout time points, and for the pre- and post-PRT time points. Post-hoc tests revealed that mean scores decreased significantly in the OB condition from 28.00 (6.4) at baseline to 19.79 (8.3) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). Mean ratings also decreased significantly in the S_15 condition from 28.50 (6.9) at baseline to 23.36 (6.8) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). No other significant changes from baseline were observed. Following the 10-puff, directed bout, the mean rating for the OB condition was significantly lower than the mean rating of 27.14 (6.5) in the U_0 condition and the mean of 26.64 (6.5) in the S_0 condition (Tukey's HSD, $p < .05$). The mean rating in the OB condition did not significantly differ from the U_15 condition's mean of 23.43 (7.0) or the S_15 condition's mean of 23.36 (6.8) following the 10-puff, directed bout.

Following the PRT, post-hoc tests revealed that mean scores decreased significantly in the OB condition from 24.57 (5.5) prior to the PRT to 12.93 (5.5) following the PRT (Tukey's HSD, $p < .05$). No other significant changes between the pre- and post-PRT time points were observed. The Factor 1 score in the OB condition was significantly lower than the U_0 condition's mean of 30.50 (4.9), the S_0 condition's mean of 27.93 (6.5), the U_15 condition's mean of 25.64 (6.6), and the S_15 condition's mean of 23.93 (6.5) following the PRT (Tukey's HSD, $p < .05$). Following the PRT, the mean score in the S_15 condition was 23.93 (6.5), significantly lower than the U_0 condition that had a mean score of 30.50 (4.9; Tukey's HSD, $p < .05$; Figure 8). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVAs revealed a significant nicotine by time interaction for the baseline and post-10-puff, directed bout time points, and a significant main effect of nicotine for the pre- and post-PRT time points, although results from the secondary, two (nicotine) by two (sucralose) ANOVA revealed a significant nicotine by sucralose interaction, post-hoc test were not able to detect any significant differences between the ECIG conditions. The main effects analyses for nicotine showed that collapsed across sucralose conditions and the pre- and post- PRT time points, the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean score of 25.79 (5.4) compared to the 0 mg/mL nicotine ECIG condition's mean score of 28.79 (5.1).

Factor 2 (Anticipation of Relief from Smoking Abstinence). The five (condition) by two (time) repeated-measures ANOVAs for Factor 2 revealed a significant condition by time interaction for the baseline and post-10-puff, directed bout time points, and for the pre- and post-PRT time points. Post-hoc tests revealed that mean scores decreased significantly in the OB condition from 15.21 (7.0) at baseline to 10.43 (4.6) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). Mean scores decreased significantly and to a similar degree to reductions observed in the OB condition, in the U_15 condition from a mean score of 15.00 (7.5) at baseline to 10.50 (4.2) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). No other significant changes from baseline were observed. Following the 10-puff, directed bout, the mean rating for the OB condition was significantly lower than the mean rating in the U_0 condition of 15.29 (7.2; Tukey's HSD, $p < .05$), but was not significantly different from the S_0 condition's mean of 14.57 (7.1), the U_15 condition's mean of 10.50 (4.2), or the S_15 condition's mean of 11.64 (4.8).

From pre- to post-PRT, post-hoc tests revealed that mean scores decreased significantly in the OB condition from 11.57 (4.7) to 7.50 (2.8; Tukey's HSD, $p < .05$). No other significant changes between the pre- and post-PRT time points were observed. Following the PRT, the mean Factor 2 score in the OB condition was significantly lower than the U_0 condition's mean of 17.71 (8.9), the S_0 condition's mean of 16.21 (8.2), the U_15 condition's mean of 13.36 (5.7), and the S_15 condition's mean of 13.07 (5.8). Following the PRT, the mean scores in the U_15 condition of 13.36 (5.7) and in the S_15 condition of 13.07 (5.8) were significantly lower than the U_0 condition's mean score of 17.71 (8.9; Tukey's HSD, $p < .05$), but not the S_0 condition's mean score of 16.21 (8.2; Figure 8). No other significant differences were observed.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVAs revealed a significant nicotine by time interaction for the baseline and post-10-puff, directed bout time points, and a significant main effect of nicotine for the pre- and post-PRT time points. However, post-hoc tests were not able to detect any significant differences between the baseline and post-bout time points between the 15 mg/mL and 0 mg/mL ECIG conditions collapsed across sucralose conditions. The nicotine main effects analyses showed that collapsed across sucralose conditions and the pre- and post- PRT time points, the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean score of 13.43 (5.4) compared to the 0 mg/mL nicotine ECIG condition's mean score of 16.43 (6.8).

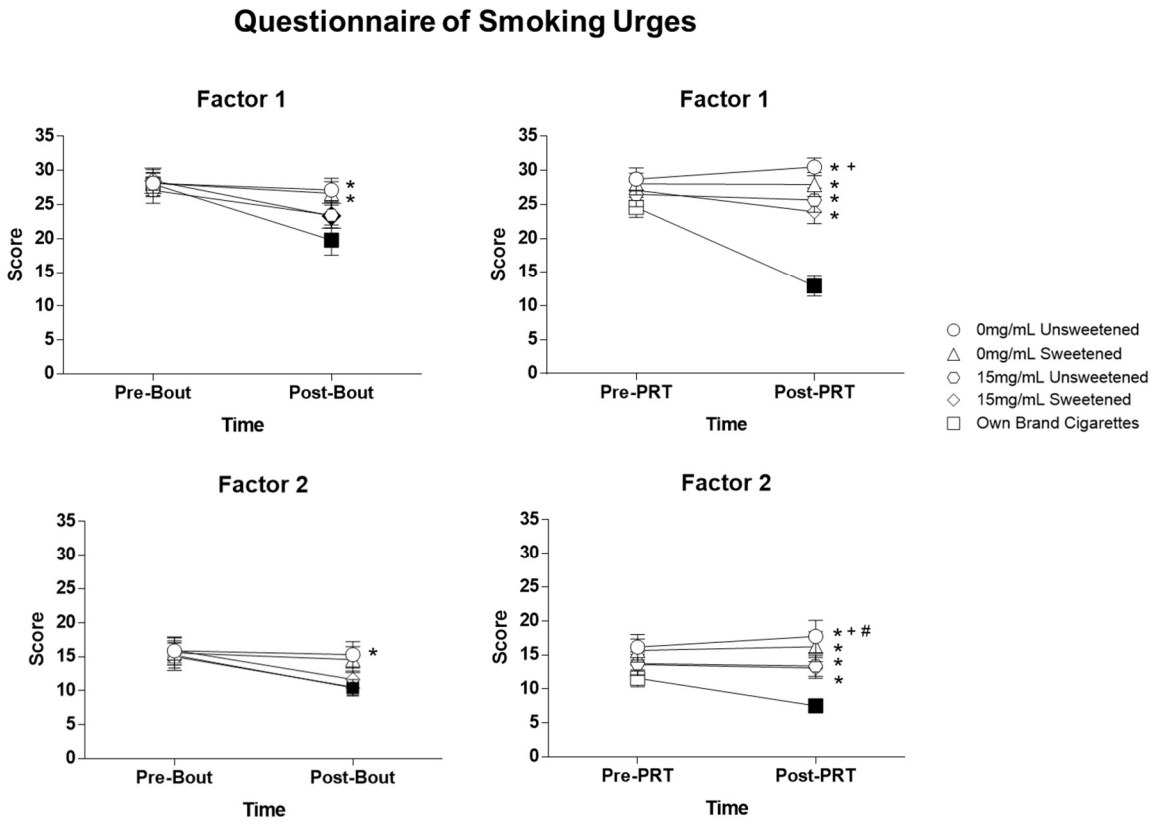

Figure 8. Mean (± SEM) QSU Factor 1 and Factor 2 scores across time for 14 cigarette smokers. Participants rated ten individual items on a seven-point Likert scale. Items were scored (scale range 0 – 35) into two aspects of smoking cravings: a desire and intention to smoke (Factor 1) and anticipation of relief from smoking abstinence (Factor 2). In all other respects, the figure is identical to Figure 3.

Positive and Negative Affect Schedule (PANAS).

Positive Affect Score. The five (condition) by two (time) repeated-measures ANOVA for the PANAS positive affect score revealed a significant interaction of condition by time for the baseline and post-10-puff, directed bout time points, and a significant main effect of time for the pre- and post-PRT time points. However, post-hoc tests were not able to detect any significant changes from baseline or differences between the conditions. The main effect analysis for time revealed that collapsed across conditions, participants' scores increased significantly from the time point prior to the PRT to the time point following the PRT. No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant interaction of sucralose by time for the baseline and post-10-puff, directed bout time points, and a significant main effect of time for the pre- and post-PRT time points. However, post-hoc tests were not able to detect any significant changes from baseline or between the sucralose-sweetened and unsweetened ECIG conditions collapsed across nicotine conditions. The main effect analyses for time revealed that collapsed across ECIG conditions, participants' scores significantly increased from the time point prior to the PRT to the time point following the PRT.

***Negative Affect Score*.** The five (condition) by two (time) repeated-measures ANOVA for the PANAS negative affect score revealed a significant main effect of time for the pre- to post-PRT time points. The main effects analysis for time showed that collapsed across conditions, participants' scores significantly decreased from the time point prior to the PRT to the time point following the PRT. No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of nicotine for the pre- and post-PRT time

points. The main effects analyses for nicotine showed that collapsed across sucralose conditions and the pre- and post- PRT time points, the 15 mg/mL nicotine-containing ECIG conditions had a significantly lower mean score of 12.11 (1.8) compared to the 0 mg/mL nicotine ECIG condition's mean score of 13.16 (3.0).

Cigarette Evaluation Questionnaire (CEQ).

Was the product satisfying?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Was the product satisfying?" revealed a significant effect of condition [F (4, 52) = 28.79, $p < .001$, $\eta_p^2 = .69$]. Post-hoc tests revealed that the mean satisfying rating in the OB condition was 6.07 (0.9), significantly greater than the U_0 condition's mean of 2.43 (0.9), the S_0 condition's mean of 2.86 (1.4), the U_15 condition's mean of 2.86 (1.1), and the S_15 condition's mean of 3.64 (1.3; Tukey's HSD, $p < .05$; Figure 9). The mean rating in the S_15 condition was significantly greater than the U_0 condition (Tukey's HSD, $p < .05$). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of sucralose. The main effects analysis showed that the sucralose-containing ECIG conditions had a significantly greater mean rating of 3.25 (1.1) compared to the unsweetened ECIG condition's mean rating of 2.64 (0.9).

Did the product taste good?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did the product taste good?" revealed a significant effect of condition [F (4, 52) = 10.07, $p < .001$, $\eta_p^2 = .44$]. Post-hoc tests revealed that the mean rating in the OB condition was 5.21 (1.3), and was significantly greater than the U_0 condition's mean of 2.71 (1.1), the S_0 condition's mean of 3.64 (1.6), the U_15 condition's mean of 2.71 (1.3), and the

S_15 condition's mean of 3.50 (1.6; Tukey's HSD, $p < .05$; Figure 9). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of sucralose. The main effects analysis showed that the sucralose-containing ECIG conditions had a significantly greater mean rating of 3.57 (1.2) compared to the unsweetened ECIG condition's mean that was 2.71 (1.0).

Did you enjoy the sensations in your throat and chest?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did you enjoy the sensations in your throat and chest?" revealed a significant effect of condition [F (4, 52) = 16.91, $p < .001$, $\eta_p^2 = .57$]. Post-hoc tests revealed that the mean rating in the OB condition was 5.36 (1.3), significantly greater than the U_0 condition's mean of 2.50 (1.0), the S_0 condition's mean of 2.64 (1.2), the U_15 condition's mean of 2.07 (0.9), and the S_15 condition's mean of 2.64 (1.6; Tukey's HSD, $p < .05$; Figure 9). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Did using the product calm you down?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product calm you down?" revealed a significant effect of condition [F (4, 52) = 14.80, $p < .001$, $\eta_p^2 = .53$]. Post-hoc tests revealed that the mean rating in the OB condition was 5.07 (1.5), significantly greater than the U_0 condition's mean of 2.14 (1.0), the S_0 condition's mean of 2.14 (1.4), the U_15 condition's mean of 2.57 (1.1), and the S_15 condition's mean of 3.14 (1.5; Tukey's HSD, $p < .05$; Figure 9). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Did using the product make you feel more awake?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product make you feel more awake?" revealed a significant effect of condition [F (4, 52) = 12.25, $p < .001$, $\eta_p^2 = .49$]. Post-hoc tests revealed that the mean rating in the OB condition was 4.14 (1.6), significantly greater than the U_0 condition's mean of 1.71 (0.9), the S_0 condition's mean of 2.07 (1.4), and the U_15 condition's mean of 1.93 (1.2; Tukey's HSD, $p < .05$), but not the S_15 condition's mean of 3.07 (1.2; Figure 9). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant interaction of nicotine and sucralose. Post-hoc tests revealed that the S_15 condition mean rating of 3.07 (1.2) was significantly greater than the U_0 condition mean of 1.71 (0.9), the S_0 condition's mean of 2.07 (1.4), and the U_15 condition's mean of 1.93 (1.2; Tukey's HSD, $p < .05$).

Did using the product make you feel less irritable?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product make you feel less irritable?" revealed a significant effect of condition [F (4, 52) = 4.91, $p < .01$, $\eta_p^2 = .27$]. Post-hoc tests revealed that the mean rating in the OB condition was 3.57 (1.6), significantly greater than the U_0 condition's mean of 1.93 (1.1) and the U_15 condition's mean of 1.86 (1.2; Tukey's HSD, $p < .05$; Figure 9), but not the S_0 condition's mean of 2.14 (1.3) or the S_15 condition's mean of 2.21 (1.5). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Did using the product help you concentrate?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product help you concentrate?"

revealed a significant effect of condition [F (4, 52) = 6.99, $p < .01$, $\eta_p^2 = .35$]. Post-hoc tests revealed that the mean rating in the OB condition was 3.43 (1.8), significantly greater than the U_0 condition's mean of 1.64 (1.0), the S_0 condition's mean of 1.79 (1.0), the U_15 condition's mean of 1.93 (1.3), and the S_15 condition's mean of 2.14 (1.3; Tukey's HSD, $p < .05$; Figure 9). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Did using the product reduce your hunger for food?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product reduce your hunger for food?" revealed a significant effect of condition [F (4, 52) = 4.02, $p < .01$, $\eta_p^2 = .24$]. Post-hoc tests revealed that the mean rating in the OB condition was 2.93 (1.6), significantly greater than the U_0 condition's mean of 1.57 (1.2), the S_0 condition's mean of 1.79 (1.0) and the U_15 condition's mean of 1.79 (1.1; Tukey's HSD, $p < .05$), but not the S_15 mean of 2.21 (1.1; Figure 9). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Did using the product make you dizzy?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product make you dizzy?" revealed a significant effect of condition [F (4, 52) = 3.85, $p < .05$, $\eta_p^2 = .23$]. However, post-hoc tests were not able to detect any significant differences between conditions.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of nicotine. The main effects analysis of nicotine showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean

rating of 2.14 (0.9) compared to the 0 mg/mL nicotine ECIG condition's mean that was 1.39 (0.7).

Did using the product make you nauseous?. The single-factor (condition) repeated-measures ANOVA for the item "Did using the product make you nauseous?" did not detect any significant effects [F (4, 52) = 1.00, $p > .05$, $\eta_p^2 = .07$]. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Did using the product immediately relieve your craving for a cigarette?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did using the product immediately relieve your craving for a cigarette?" revealed a significant effect of condition [F (4, 52) = 19.88, $p < .001$, $\eta_p^2 = .61$]. Post-hoc tests revealed that the mean rating in the OB condition was 5.50 (1.6), significantly greater than the U_0 condition's mean of 1.79 (1.0), the S_0 condition's mean of 2.29 (1.3), the U_15 condition's mean of 2.86 (1.3), and the S_15 condition's mean of 2.79 (1.5; Tukey's HSD, $p < .05$). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Did you enjoy using the product?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Did you enjoy using the product?" revealed a significant effect of condition [F (4, 52) = 19.27, $p < .001$, $\eta_p^2 = .60$]. Post-hoc tests revealed that the mean rating in the OB condition was 6.07 (1.0), significantly greater than the U_0 condition's mean of 3.14 (1.0), the S_0 condition's mean of 3.14 (1.7), the U_15 condition's mean of 2.57 (1.2), and the S_15 condition's mean of 3.36 (1.6; Tukey's HSD, $p < .05$). No other significant differences

were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

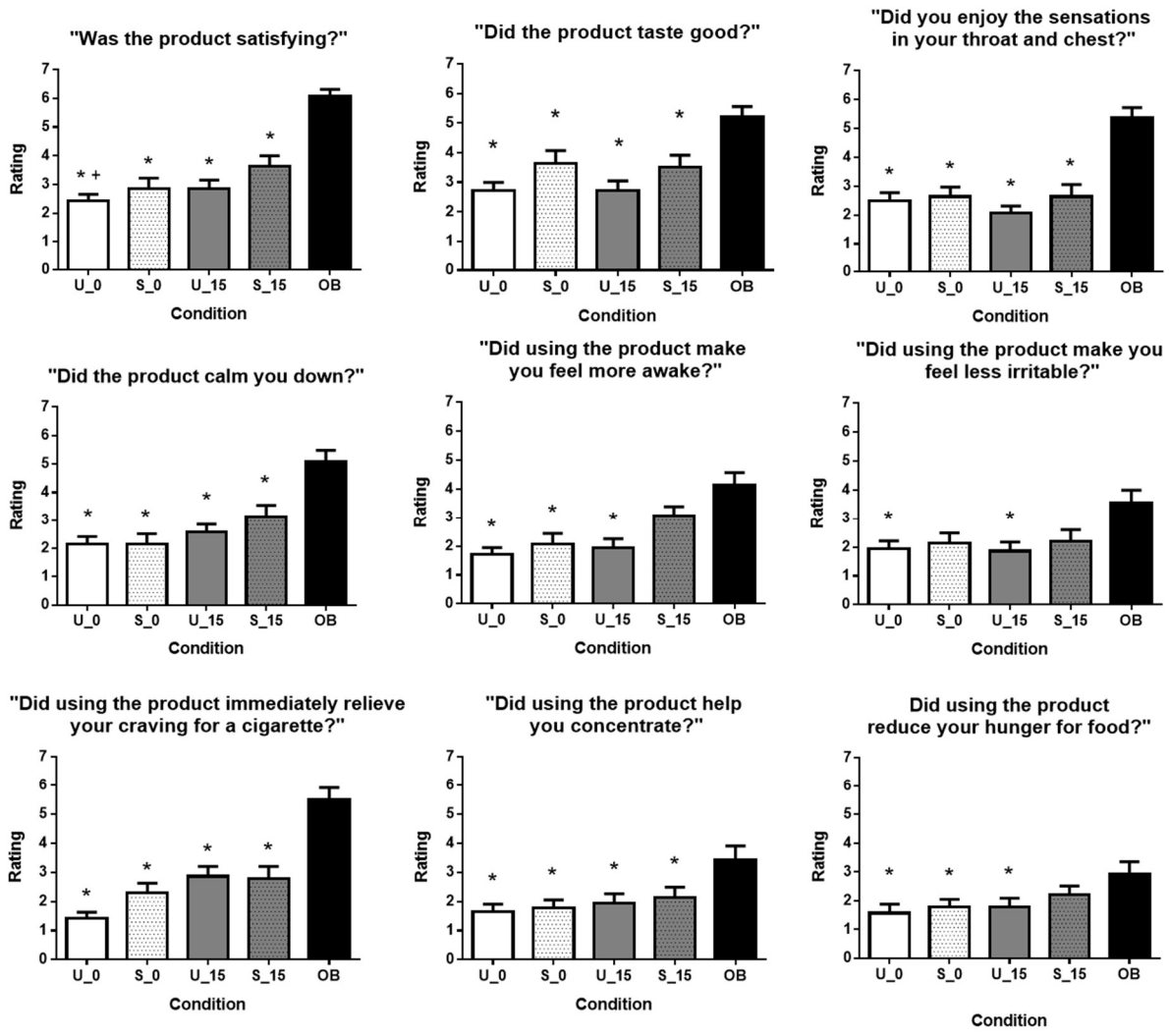

Figure 9. Mean ratings (+SEM) for the CEQ subjective items "Was the product satisfying?", "Did the product taste good?", "Did you enjoy the sensations in your throat and chest?", "Did the product calm you down?", "Did using the product make you feel more awake?", "Did using the product make you feel less irritable?", "Did using the product immediately relieve your craving for a cigarette?", "Did using the product help you concentrate?", and "Did using the product reduce your hunger for food?" for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

Drug Effects Questionnaire (DEQ).

Do you feel a drug effect right now?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Do you feel a drug effect right now?" revealed a significant effect of condition [F (4, 52) = 8.47, $p < .001$, $\eta_p^2 = .39$]. Post-hoc tests revealed that the mean rating in the OB condition of 47.14 (31.5) was significantly greater than the U_0 condition's mean of 14.64 (17.7) and the S_0 condition's mean of 14.57 (23.8; Tukey's HSD, $p < .05$), but was not significantly different from the mean rating in the U_15 condition of 33.93 (23.5) or the mean rating in the S_15 condition of 35.14 (31.5). The mean rating in the S_15 condition was significantly greater than the U_0 and the S_0 condition's means (Tukey's HSD, $p < .05$; Figure 10). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of nicotine. The main effects analysis showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean rating of 34.54 (22.0) compared to the 0 mg/mL nicotine ECIG condition's mean rating that was 14.61 (16.2).

Do you like any of the effects [that] you are feeling right now?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Do you like any of the effects [that] you are feeling right now?" revealed a significant effect of condition [F (4, 52) = 7.27, $p < .001$, $\eta_p^2 = .36$]. Post-hoc tests revealed that the mean rating in the OB condition was 73.57 (16.6), significantly greater than the U_0 condition's mean of 36.21 (19.9), the S_0 condition's mean of 37.79 (29.3), the U_15 condition's mean of 49.43 (18.9), and the S_15 condition's mean of 47.14 (21.1; Tukey's HSD, $p < .05$; Figure 10). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

Do you dislike any of the effects [that] you are feeling right now?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Do you dislike any of the effects [that] you are feeling right now?" did not detect any significant interactions or main effects [F (4, 52) = 0.99, $p > .05$, η_p^2 =.07]. Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Do you have a rush/buzz right now?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Do you have a rush/buzz right now?" revealed a significant effect of condition [F (4, 52) = 4.96, $p < .01$, η_p^2 = .28]. Post-hoc tests revealed that the mean rating in the OB condition was 45.43 (32.4) and was significantly greater than the U_0 condition's mean of 16.50 (20.7) and the S_0 condition's mean of 17.86 (25.7; Tukey's HSD, $p < .05$), but not the U_15 condition's mean of 33.64 (25.4) or the S_15 condition's mean of 34.36 (23.3; Figure 10). No other significant differences between conditions were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of nicotine. The main effects analysis showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean rating of 34.00 (20.0) compared to the 0 mg/mL nicotine ECIG condition's mean rating that was 17.18 (18.8).

Would you like more of the product you used, right now?. The single-factor (condition) repeated-measures ANOVA for the subjective item "Would you like more of the product you used, right now?" revealed a significant effect of condition [F (4, 52) = 10.50, $p < .001$, η_p^2 = .45]. Post-hoc tests revealed that the mean the rating in the OB condition was 78.14 (21.5), significantly greater than the U_0 condition's mean of 28.43 (22.0), the S_0 condition's mean of 39.00 (35.4), the U_15 condition's mean of 34.71 (25.9), and the S_15 condition's mean of 49.00 (27.3; Tukey's HSD, $p < .05$; Figure 10). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of sucralose. The main effects analysis showed that the sucralose-containing ECIG conditions had a significantly greater mean rating of 44.0 (27.5) compared to the unsweetened ECIG conditions' mean rating that was 31.57 (19.5).

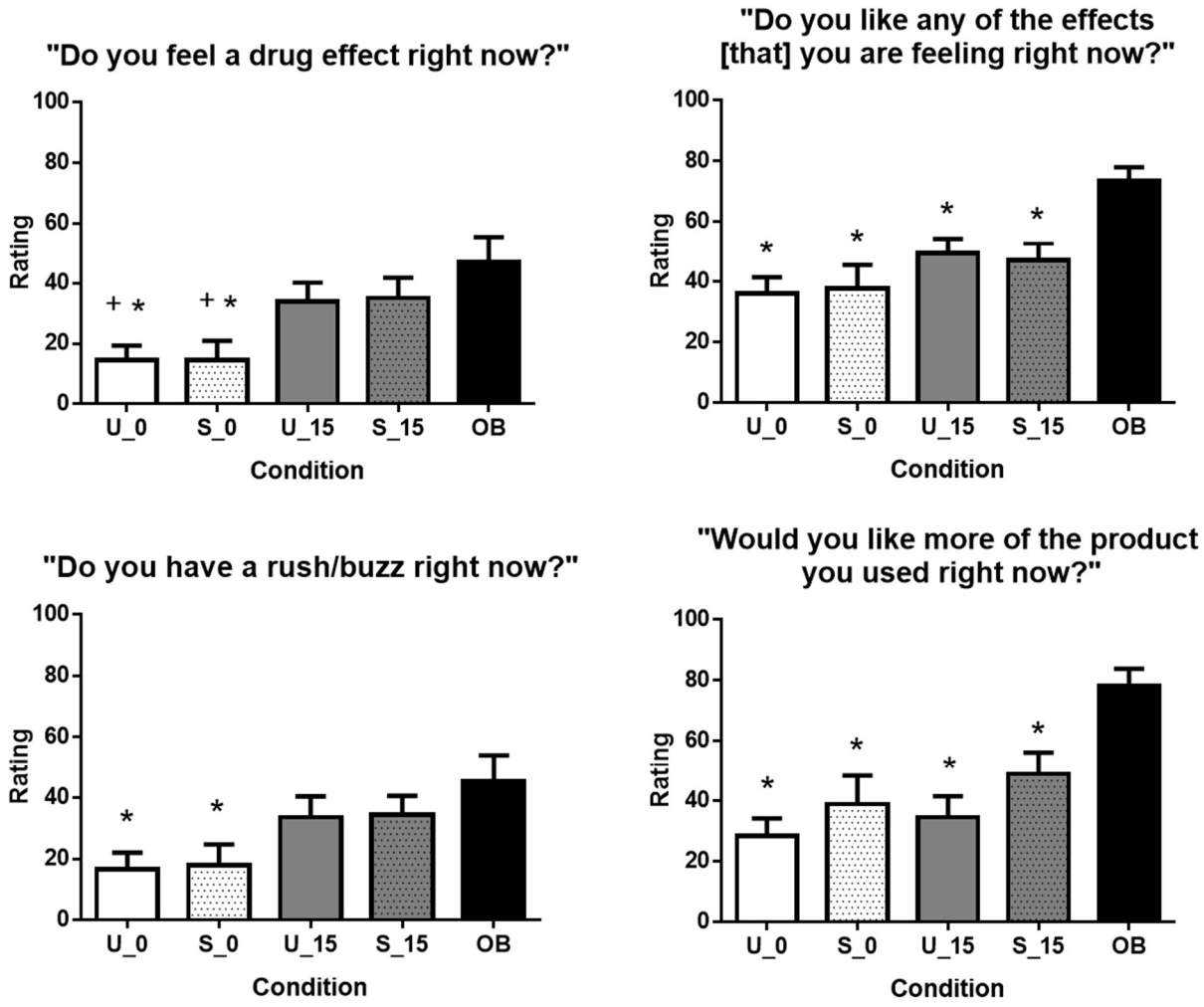

Figure 10. Mean (+SEM) ratings for the DEQ subjective items "Do you feel a drug effect right now?", "Do you like any of the effects [that] you are feeling right now?", "Do you have a rush/buzz right now?", and "Would you like more of the product you used right now?" for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

Direct Effects of Nicotine (DEN) Scale.

Dizzy. The five (condition) by two (time) repeated-measures ANOVA revealed a significant condition by time interaction for the item "Dizzy". Post-hoc analyses revealed that mean dizzy ratings significantly increased in the OB condition from 4.14 (7.0) at baseline to 25.21 (30.6) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). Following the 10-puff, directed bout, the mean rating for the OB condition was significantly greater than the U_0 condition's mean of 3.86 (7.0) and the S_0 condition's mean of 3.14 (4.0; Tukey's HSD, $p < .05$), but not significantly greater than the U_15 condition's mean of 10.64 (12.7) or the S_15 condition's mean of 12.64 (17.8; Figure 11). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant interaction of nicotine by time. Post-hoc tests revealed that collapsed across sucralose conditions, the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean rating of 11.64 (14.0) following the 10-puff, directed bout compared to the 0 mg/mL nicotine ECIG conditions mean rating of 3.50 (5.04) following the 10-puff, directed bout. No other significant differences were observed.

Confused. The five (condition) by two (time) repeated-measures ANOVA for the subjective item "Confused" did not detect any significant interactions or main effects. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Excessive Salivation. The five (condition) by two (time) repeated-measures ANOVA for the item "Excessive salivation" revealed a significant effect of condition. However, post-hoc test were not able to detect any significant differences between conditions collapsed across time

points. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA did not detect any significant interactions or main effects.

Headache. The five (condition) by two (time) repeated-measures ANOVA for the subjective item "Headache" did not detect any significant interactions or main effects. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Heart-pounding. The five (condition) by two (time) repeated-measures ANOVA for the item "Heart-pounding" revealed a significant main effect of time. Collapsed across conditions, participants' scores significantly increased from baseline following the 10-puff, directed bout. No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA revealed a significant main effect of time for mean rating for the item heart-pounding. The main effects analysis for time showed that the baseline mean rating had a significantly lower mean rating of 3.52 (5.0) compared to the post directed bout's mean rating that was 7.23 (8.1).

Lightheaded. The five (condition) by two (time) repeated-measures ANOVA for the item "Lightheaded" revealed a significant condition by time interaction. Post-hoc analyses revealed that mean lightheaded ratings increased significantly in the OB condition from 5.50 (8.70) at baseline to 30.50 (32.18) following the 10-puff, directed bout (Tukey's HSD, $p < .05$). Following the 10-puff, directed bout, the OB condition's mean rating was significantly greater than the U_0 condition's mean of 11.00 (18.4), the S_0 condition's mean of 6.36 (6.8), and the U_15 condition's mean of 11.7 (15.2; Tukey's HSD, $p < .05$; Figure 11). No other significant differences were detected. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA did not detect any significant interactions or main effects.

Nauseous. The five (condition) by two (time) repeated-measures ANOVA for the item "Nauseous" did not detect any significant interactions or main effects. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Nervous. The five (condition) by two (time) repeated-measures ANOVA did not detect any significant interactions or main effects for the subjective item "Nervous". Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Sweaty. The five (condition) by two (time) repeated-measures ANOVA for the subjective item "Sweaty" did not detect any significant interactions or main effects. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Weak. The five (condition) by two (time) repeated-measures ANOVA for the subjective item "Weak" did not detect any significant interactions or main effects. Results from the secondary, two (nicotine) by two (sucralose) by two (time) repeated-measures ANOVA also did not detect any significant interactions or main effects.

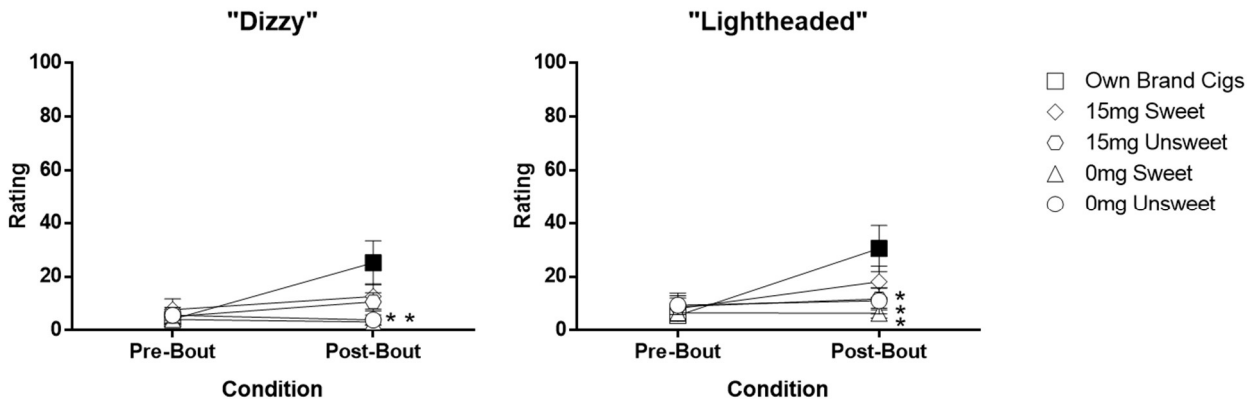

Figure 11. Mean (± SEM) ratings from the DEN for the subjective items "Dizzy" and "Lightheaded" across time for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

General Labeled Magnitude Scale (GLMS).

How would you describe the overall sweetness of the product you just used?. After logarithmically transforming the data, the single-factor (condition) repeated-measures ANOVA for sweetness revealed a significant effect of condition [F (4, 52) = 4.02, $p < .01$, $\eta_p^2 = .24$]. Post-hoc tests revealed that the mean rating in the U_0 condition was 0.72 (1.2), significantly lower than the S_15 condition's mean of 1.52 (0.3; Tukey's HSD, $p < .05$; Figure 12). There were no significant differences detected between the S_0 condition's mean of 1.31 (0.7), the U_15 condition's mean of 1.44 (0.3), or the OB condition's mean of 0.87 (1.1). No other significant differences were observed.

Results from the secondary, two (nicotine) by two (sucralose) ANOVA revealed significant main effects of nicotine and sucralose. The main effects analysis for sucralose showed that the sucralose-containing ECIG conditions had a significantly greater mean rating of 1.42 (0.4) compared to the unsweetened ECIG conditions' mean that was 1.08 (0.7). The main effects analysis for nicotine also showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean rating of 1.48 (0.3) compared to the 0 mg/mL nicotine ECIG conditions' mean that was 1.01 (0.8).

How would describe the overall harshness/irritancy of the product you just used?. After logarithmically transforming the data, the single-factor (condition) repeated-measures ANOVA for the subjective rating of harshness revealed a significant effect of condition [F (4, 52) = 4.33, $p < .05$, $\eta_p^2 = .10$]. Post-hoc tests revealed that the mean rating in the OB condition was 0.81 (1.0) and was significantly lower than the U_15 condition's mean of 1.57 (0.4) and the S_15 condition's mean of 1.59 (0.3; Tukey's HSD, $p < .05$; Figure 12). No other significant differences were detected.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of nicotine for the subjective rating of harshness. The main effects analysis showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean rating of 1.58 (0.3) compared to the 0 mg/mL nicotine ECIG condition's mean that was 1.17 (0.7).

How would you describe the overall throat hit of the product you just used?. After logarithmically transforming the data, the single-factor (condition) repeated-measures ANOVA for the subjective log rating of throat hit revealed a significant effect of condition [F (4, 52) = 3.35, $p < .05$, $\eta_p^2 = .21$]. However, post-hoc tests were not able to detect any significant differences in ratings between any of the conditions.

Results from the secondary, two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant main effect of nicotine for throat hit. The main effects analysis showed that the 15 mg/mL nicotine-containing ECIG conditions had a significantly greater mean rating of 1.70 (0.2) compared to the 0 mg/mL nicotine ECIG conditions' mean that was 1.35 (0.3).

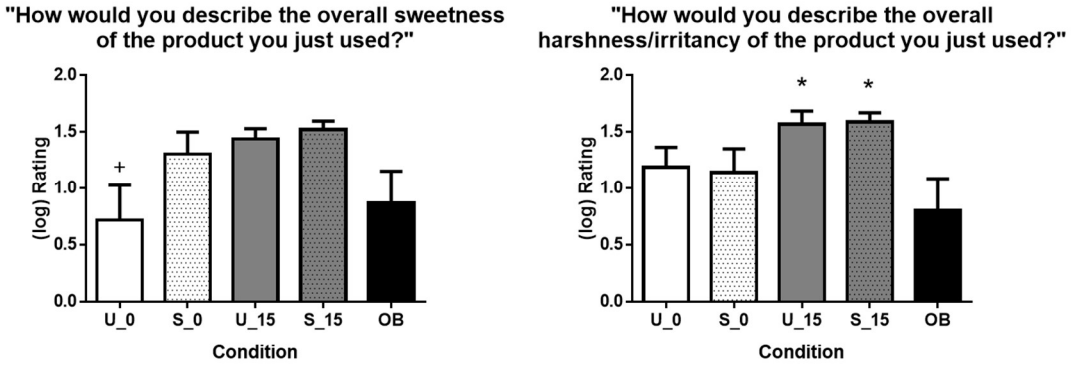

Figure 12. Mean (+ SEM) rating (log transformed) for the GLMS subjective items "How would you describe the overall sweetness of the product you just used?" and "How would you describe the overall harshness/irritancy of the product you just used?" for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3.

Labeled Hedonic Scale (LHS).

The single-factor (condition) repeated-measures ANOVAs did not any detect any significant effects on ratings of liking/disliking for the subjective items for "How would you describe the overall sweetness of the product you just used?" [F (4, 52) = 0.58, $p > .05$, η_p^2 = .04], "How you would describe the overall harshness/irritancy of the product you just used?" [F (4, 52) = 1.45, $p > .05$, η_p^2 = .10], or "How would you describe the overall throat hit of the product you just used?" [F (4, 52) = 2.00, $p > .05$, η_p^2 = .13]. Results from the two (nicotine) by two (sucralose) repeated-measures ANOVAs also did not reveal any significant interactions or main effects.

Willingness to use again questions (WUA).

How likely would you be to use this product again if it was offered to you by a close friend?. The single-factor (condition) repeated-measures ANOVA for the subjective rating of willingness to use the product again from a friend revealed a significant effect of condition [F (4, 52) = 21.13, $p < .001$, η_p^2 = .62]. Post-hoc tests revealed that the mean rating in the OB condition was 92.79 (7.7), significantly greater than the U_0 condition's mean of 30.93 (24.1), the S_0 condition's mean of 32.43 (30.4), the U_15 condition's mean of 21.93 (26.01), and the S_15 condition's mean of 42.50 (28.0; Tukey's HSD, $p < .05$; Figure 13). No other significant differences were detected.

Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA revealed a significant interaction of nicotine and sucralose for the subjective rating of willingness to use the product again from a friend. Post-hoc tests revealed that the U_15 condition's mean rating of 21.93 (26.0) was significantly lower than the S_15 condition's mean rating of 42.50 (28.0; Tukey's HSD, $p < .05$). No other significant differences were observed.

How likely would you be to buy this product for personal use?. The single-factor (condition) repeated-measures ANOVA for the subjective rating of willingness to buy this product for personal use revealed a significant effect of condition [F (4, 52) = 42.32, $p < .001$, $\eta_p^2 = .77$]. Post-hoc tests revealed that the mean rating in the OB condition was 91.93 (10.7), significantly greater than the U_0 condition's mean of 13.43 (12.1), the S_0 condition's mean of 18.71 (27.1), the U_15 condition's mean of 12.93 (18.7), and the S_15 condition's mean of 25.43 (27.9 Tukey's HSD, $p < .05$; Figure 13). No other significant differences were detected. Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA did not detect any significant interactions or main effects.

How likely would you be to recommend this product to a smoker who is trying to reduce or quit smoking?. The single-factor (condition) repeated-measures ANOVA effects for the subjective rating of recommending the product for smoking cessation did not detect any significant effects [F (4, 52) = 2.23, $p > .05$, $\eta_p^2 = .15$]. Results from the two (nicotine) by two (sucralose) repeated-measures ANOVA also did not detect any significant interactions or main effects.

Do you think there was nicotine in the product you used today?. For the item "Do you think there was nicotine in the product you used today?", 28.6% of participants thought that there was nicotine in the U_0 condition, 42.9% thought that there was nicotine in the S_0 condition, 85.7% thought that there was nicotine in the U_15 condition, 85.7% thought that there was nicotine in the S_15 condition, and 100% thought that there was nicotine in the OB condition (Figure 13).

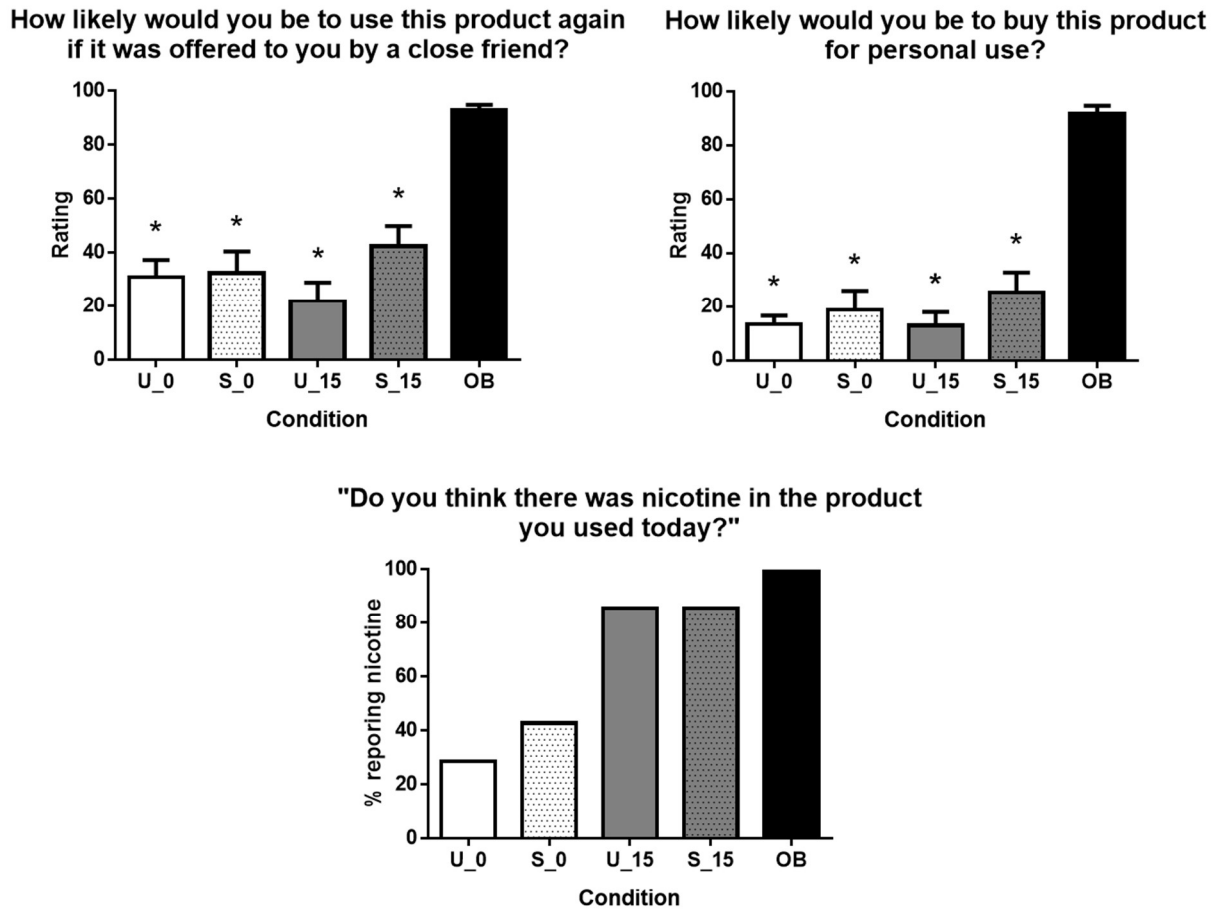

Figure 13. Top row depicts mean (+SEM) ratings for the subjective items "How likely would you be to use this product again if it was offered to you by a close friend?" and "How likely would you be to buy this product for personal use?" for 14 cigarette smokers. In all other respects, the figure is identical to Figure 3. Bottom panel depicts percentage of participants reporting nicotine present in the product they used by condition.

Discussion

Overview

ECIGs are a heterogeneous class of tobacco products that have become popular over the past decade (e.g., Breland et al., 2017). One feature that makes these tobacco products so appealing – in addition to the fact that they can deliver nicotine to the user – is that the nicotine liquids used in them are often flavored (Zhu et al., 2014), and many of those flavors include sweeteners (Fagan et al., 2018). Unfortunately, these appealing features – nicotine delivery, flavorants, and sweeteners, have led to widespread abuse of ECIGs by youth and young adults (Cornelius et al., 2020; Mayer et al., 2020). As of 2016, ECIGs are regulated in the U.S. by the FDA's Center for Tobacco Products (81 FR 28974), therefore, the FDA has the authority to address ECIG abuse among youth and young adults by reducing ECIG abuse liability – the likelihood that an ECIG will sustain long-term use. The FDA's regulation of ECIGs is made challenging by the heterogeneity of the product class and the many flavorants added to the liquids. However, the fact that many flavored ECIG liquids are also sweetened with a limited number of compounds such as sucralose, ethyl maltol, and sorbitol (Fagan et al., 2018; Miao et al., 2016) suggests a potential method for reducing ECIG abuse liability systematically: eliminate sweeteners. Such an approach may protect nicotine-naive youth and young adults from acquiring nicotine dependence by reducing the appeal of repeated ECIG use, while preserving the potential for ECIGs to help cigarette smokers quit combustible cigarettes. While this approach appears appropriate for FDA's mission to protect the public health of tobacco product users and non-users, there is a lack of data to support it. That is, to date, there has been no systematic evaluation of the abuse liability of unsweetened and sweetened, flavorless ECIG liquids. The clinical laboratory offers efficient methods for assessing the abuse liability of tobacco products (Breland

et al., 2020; Cobb et al., 2019; Hiler et al., 2017; Lopez et al., 2016; Maloney et al., 2019; Maloney et al., 2021; Vansickel et al., 2012) and can be used to address this regulatory science gap. Clinical laboratory abuse liability assessments include a combination of measures, including nicotine delivery profile, responses on behavioral assessments of drug seeking and reward, and subjective effects. Thus, the clinical laboratory provides an opportunity for a multi-dimensional understanding of a tobacco product's abuse liability that can inform regulation. Therefore, the aim of this study was to evaluate the effects of a sweetener (sucralose) and nicotine in otherwise unflavored ECIG liquids using multiple measures relevant to abuse liability, such as nicotine delivery profile, user behavior (i.e., puff topography), behavioral measures of reinforcement, and subjective effects. Results inform a basic understanding of the influence of ECIG sweeteners on ECIG abuse liability.

Nicotine Delivery and User Behavior (Puff Topography)

Evaluating a tobacco product's nicotine delivery profile is relevant to understanding that product's abuse liability (Carter et al., 2009; Henningfield & Keenan, 1993; Henningfield et al., 1985). Like with most psychoactive drugs, as nicotine dose and rate of delivery increases, the rewarding effects and the likelihood for the drug, or drug product, to be abused also increases (Jaffe & Jaffe, 1989; Henningfield et al., 1985; Henningfield & Keenan, 1993; Perkins et al., 1994). Assessment of nicotine delivery in the current study demonstrated that when participants took 10 puffs (30 sec IPI) from a 30 W ECIG paired with a 15 mg/mL nicotine-containing liquid, plasma nicotine concentration increased, though not to the same degree observed after 10 puffs from an OB combustible cigarette. That is, plasma nicotine increased by 7.09 ng/mL in the U_15 condition and 5.85 ng/mL in the S_15 condition, relative to 12.32 ng/mL in the OB condition. As expected, plasma nicotine concentration did not increase in either of the two 0 mg/mL nicotine

conditions (see Figure 3). This failure of the ECIG device/liquid in this study to deliver nicotine as effectively as an OB cigarette is similar to previous reports involving multiple ECIG products with similar puffing procedures (e.g., Lopez et al., 2016; Maloney et al., 2019; Maloney et al., 2021; O'Connell et al., 2019; Campbell et al., 2022). However, other studies with similar puffing procedures, but different ECIG/liquid combinations, do report cigarette-like nicotine delivery, though in these reports study participants were often experienced ECIG users (e.g., Hajek et al., 2020; Hiler et al., 2017; Hiler et al., 2020; Wagener et al., 2017). This observation that experience with ECIG use influences the nicotine delivery profile of an ECIG device/liquid combination likely is explained by the fact that experienced ECIG users take longer puffs from an ECIG device (e.g., 5.3 sec) than do ECIG-inexperienced combustible cigarette smokers (e.g., 2.8 sec; Hiler et al., 2017). Thus, the abuse liability of any ECIG device/liquid combination is likely a function of the combined influence of device characteristics (e.g., power output), liquid constituents (e.g., nicotine concentration), and user behavior (i.e., puff duration).

In fact, puff topography was measured in the current study, and results are consistent with Hiler et al's (2017) demonstration that the ECIG-inexperienced combustible cigarette smokers in this study took relatively short puffs when using the ECIG provided to them. That is, the mean puff duration in the U_15 condition was 1.60 sec and in the S_15 condition was 1.94 sec; mean puff duration in the OB combustible cigarette condition was 2.06 sec. Thus, the nicotine delivery profile in the study was likely influenced by the inexperience of study participants with ECIGs generally.

When comparing the ECIG conditions, puff duration was influenced by nicotine and sucralose. Collapsed across sucralose conditions, when participants used an ECIG in a condition that contained nicotine, they took puffs of significantly shorter puff duration (M = 1.77)

compared to when they used an ECIG condition without nicotine (*M* = 2.64). Collapsed across nicotine conditions, when participants used an ECIG with sucralose, they took puffs of significantly longer mean puff duration (*M* = 2.34) compared to when they used an unsweetened ECIG condition (*M* = 2.07). A similar pattern of results was observed for puff volume (see Figure 4). Taken together, these results support the notion that sweetening ECIG liquids may enhance overall abuse liability by increasing the likelihood of longer and larger puffs which, in turn, increases the likelihood of greater nicotine delivery.

Behavioral Assessments

The CPT, CP-CPT, and PRT were used to measure the hypothetical demand and reinforcing efficacy of the study products. The CPT and the CP-CPT were administered 25 minutes following the 10-puff, directed bout. Results from the CPT revealed that the mean intensity, or amount of product consumption when the product was free, was greatest in the OB condition. Mean intensity in the OB condition was 15.29, significantly greater than the U_0 condition' mean of 8.50, the S_0 condition's mean of 9.86, the U_15 condition's mean of 8.71, and the S_15 condition's mean of 8.36, demonstrating that participants would smoke more cigarettes given free access to the product compared to the ECIG conditions. Although there was no significant difference between ECIG conditions on this measure, participants indicated that they would take approximately eight puffs of any of the ECIG conditions if the ECIG puffs were free of charge and were the only tobacco products available on the market, suggesting that all of the ECIG conditions have some degree of reinforcing efficacy. Participants' mean O_{max}, or maximum amount of money participants were willing to spend on a day's use of the study product on the CPT, was $6.39 in the OB condition, significantly greater than the ECIG conditions (range of means: $2.14 - $3.54; Figure 5). While OB had the highest demand and

reinforcing efficacy on the CPT in the current study, the ECIG conditions that contained nicotine had a significantly greater O_{max} compared to the ECIG conditions without nicotine, suggesting that nicotine-containing ECIG conditions had a higher demand and reinforcing efficacy than non-nicotine containing ECIG conditions. Notably, there was no detectable influence of sucralose on demand indices of abuse liability as measured by the CPT.

Overall, the ECIG conditions examined in the current study had lower CPT breakpoint (M = 1.74 vs. M = 3.37), O_{max} (M = 3.51 vs. M = 8.74), and P_{max} (M = 0.92 vs. M = 2.62) values compared to previous reports (Barnes et al., 2017). This finding could suggest that the ECIG conditions examined in this study were of lower abuse liability than ECIG conditions previously studied, or may be related to a failure of specific ECIG device/liquid combinations to match the nicotine delivery profile of a combustible cigarette, which, of course, is influenced by device features, liquid nicotine concentration, and user behavior. However, it also could be due participants' in the current study having a more limited disposable income as 64% were unemployed at the time of participation, discussed in further details in the limitations.

Cross-price intensity comparisons revealed that almost half of the participants were willing to purchase puffs from the U_0, the S_0, and the S_15 conditions when OB cigarettes were free on the CP-CPT, but only about a quarter of participants were willing to purchase puffs from the U_15 condition when OB cigarettes were free (see Table 6). Participants' cross-price elasticity was negative and close to zero in all four ECIG conditions, suggesting that the ECIGs in the current study may serve as very weak cigarette compliments rather than cigarette substitutes. Again, these results may reflect the fact that in the current study the ECIG device/liquid combinations failed to achieve the same nicotine delivery profile as participants' OB combustible cigarettes. Also, unlike in previous work using this measure (Stein et al., 2018),

the current study did not include flavored (other than sucralose) ECIG liquids, and liquid flavorants may influence ECIG substitutability in cigarette smokers.

The PRT was administered approximately one hour following the 10-puff, directed bout. The results from the PRT revealed that the mean breakpoint value for the OB condition was significantly greater than the S_0 condition's and the U_15 condition's breakpoint value, but the OB condition did not differ significantly from the U_0 condition's or the S_15 condition's breakpoint. A similar pattern was observed for puffs; participants earned significantly more puffs in the OB condition (M = 9.93) than in the S_0 condition (M = 6.21 puffs) and the U_15 condition (M = 5.07 puffs), but mean puffs in the OB condition did not differ significantly from the mean puffs earned in the U_0 condition (M = 7.64 puffs) or the S_15 condition (M = 7.21 puffs; see Figure 5). Differences in breakpoint and puffs earned, or lack thereof, between the OB and the U_0 conditions and the S_15 and the U_0 conditions, may be explained partially by participants becoming satiated. Participants in the OB condition earned nearly one cigarette's worth of puffs during the PRT, and therefore, may not have been motivated to continue to work for puffs. The OB, the S_15, and the U_0 conditions facilitated responding on the PRT that would be indicative of an elevated abuse liability compared to the S_0 and the U_15 conditions. Interestingly, the breakpoint and the number of puffs earned in the U_0 condition highlights the reinforcing properties and the importance of non-nicotine smoking cues in sustaining smoking maintenance. The results from the U_0 condition also demonstrate the need for reliable nicotine delivery to cue users and extinguish nicotine- and tobacco-seeking behaviors and prevent excess toxicant exposure, as sensorimotor smoking-cues, even in the in the absence of nicotine, flavor, and sweeteners, can facilitate responding for puffs (Jackson et al., 2021). The PRT has been used in previous studies to investigate ECIGs (Audrain-McGovern et al., 2016; Copp et al., 2015;

Hoetger et al., 2021: Pacek et al., 2010). One of these studies examined the impacts of sweet-flavored ECIGs and found that participants worked significantly harder on a progressive-ratio schedule of reinforcement for sweet- (fruit or dessert) flavored puffs and earned double the number of sweet-flavored puffs compared to unflavored (no flavor) puffs despite the unflavored condition having a lower, fixed-ratio work requirement to earn puffs (Audrain-McGovern et al., 2016). Among nicotine-containing ECIGs, sweet-flavored liquids and sweeteners may increase the reinforcing efficacy of ECIGs in smokers. Interestingly, the ECIG flavor study and the current study demonstrate that unflavored, nicotine-containing ECIGs can facilitate responding on a fixed- or progressive-ratio task illustrating the impact of nicotine and smoking cues alone on ECIG abuse liability (Audrain-McGovern et al., 2016). Future clinical assessments of ECIGs would benefit from including flavorless (no flavor; just PG/VG) conditions in order to further understand how ECIG flavors and additives, other than nicotine, affect ECIG abuse liability.

Subjective Measures

The current study included subjective effects measures designed to capture drug effects, tobacco abstinence symptom suppression, product appeal, sensory attributes, intentions to use, and changes in mood. Nicotine delivery plays a pivotal role in reinforcing subjective effects of ECIGs. A good indication of nicotine delivery, is the reduction of tobacco abstinence symptoms following product use (Hiler et al., 2017). In the current study, reductions in nicotine and tobacco abstinence symptoms were the most pronounced following OB cigarette use. Participants' cigarette/nicotine cravings, urges to smoke, and tobacco abstinence symptoms, as measured by the QSU Factor 1 and Factor 2 scores in the OB condition were significantly reduced from baseline following the 10-puff, directed bout, and again following the PRT. Participants' tobacco abstinence symptom scores were significantly lower in the OB condition than in the U_0 and the

S_0 conditions following the 10-puff, directed bout and were significantly lower than all four ECIG conditions following the PRT (see Figure 8). As predicted, the OB condition suppressed nicotine and tobacco abstinence symptoms to a greater degree than any of the ECIG conditions. However, participants' QSU Factor 2 score was reduced in the U_15 condition to a similar degree as observed in the OB condition following the 10-puff, directed bout.

The nicotine-containing ECIG conditions were able to reduce tobacco abstinence symptoms following the 10-puff, directed bout, but significant decreases from prior to the PRT to following the PRT were not observed for any of the ECIG conditions. Following puffs from the U_15 condition, participants' QSU Factor 2 score and "urges to smoke" ratings were significantly reduced from baseline. Following puffs from the S_15 condition, participants' QSU Factor 1 score, and ratings of "urges to smoke" and "cigarette/nicotine cravings" were significantly reduced from baseline, and participants' QSU Factor 1 score was significantly lower in the S_15 condition compared to the U_0 condition following the 10-puff, directed bout. Although participants' "urges to smoke" ratings did not significantly decrease from prior to the PRT to following the PRT, participants' were significantly lower in the U_15 and the S_15 conditions compared to the U_0 condition following the 10-puff, directed bout, and participants' QSU Factor 2 scores were significantly lower in the U_15 and the S_15 conditions compared to the U_0 condition following the PRT (see Figure 8). Similar to previous studies, nicotine-containing ECIG conditions suppressed smokers' tobacco abstinence symptoms better than ECIG conditions without nicotine (Hiler et al., 2017; Maloney et al., 2019; Perkins et al., 2017), but these reductions were less pronounced compared to participants OB cigarettes (Cobb et al., 2019; Maloney et al., 2019). The addition of sucralose appeared to reduce "cigarette/nicotine cravings" in addition to "urges to smoke" in ECIG conditions that contained nicotine. Overall,

nicotine had the greatest impacts on tobacco abstinence suppression. Mood was assessed in the current study, and the results indicated that collapsed across conditions, participants' mean positive affect score increased and mean negative affect score decreased following product use across all conditions. Additionally, participants mean negative affect collapsed across the PRT time points and sucralose conditions, was significantly lower in the nicotine-containing ECIG conditions compared to the ECIG conditions without nicotine. Previous evaluations of ECIGs did not find changes or differences in mood following ECIG use (Cobb et al., 2019).

Results from the CEQ demonstrated that the OB condition had significantly greater ratings than all four ECIG conditions on the items "Did you enjoy the sensations in your throat and chest?", "Did using the product help you concentrate?", "Did the product taste good?", "Was the product satisfying?", "Did you enjoy using the product?", "Did using the product immediately relieve your craving for a cigarette?", and "Did the product calm you down?" (see Figure 9). Ratings for the DEQ items "Do you like any of the effects that you are feeling right now?" and "Would you like more of the product you used, right now?" were significantly greater in the OB condition compared to all four ECIG conditions. Similar to previous reports (Cobb et al., 2019), these results demonstrate that the OB condition was much more appealing than all four ECIG conditions.

Significant effects were also observed for sucralose on the CEQ. Collapsed across nicotine conditions, the ECIG conditions that contained sucralose had significantly greater mean ratings than the unsweetened ECIG conditions for the items "Would you like more of the product you used right now?", "Did the product taste good?" and "Was the product satisfying?". The S_15 condition had a significantly greater mean rating for the item "Was the product satisfying?" than the U_0 condition (see Figure 9). Thus, participants rated ECIG conditions that contained

sucralose as more appealing than ECIG conditions without sucralose. These results suggest that factors and attributes other than nicotine may play a role on initial reactions to ECIG use, especially when ECIG-delivered nicotine is low, relative to OB cigarettes.

Ratings for the DEQ items “Do you feel a drug effect right now?”, “Do you have a rush/buzz right now?”, and “Did using the product make you dizzy”, and increases in DEN item ratings of “Dizzy” following the 10-puff, directed bout were significantly greater in the OB condition and the nicotine-containing ECIG conditions compared to the ECIG conditions without nicotine. These results illustrate the impact of nicotine delivery on drug effects and were similar to previous reports of ECIG subjective effects comparisons (Cobb et al., 2019). Nicotine and sucralose increase ECIG abuse liability on measures of subjective effects, but they appear to do so through different mechanisms or factors, many of which are either directly or indirectly affected by nicotine delivery.

Ratings of sensory attributes were captured in the current study using the GLMS and the LHS. When participants were asked to describe the overall sweetness of the products they used, they rated the S_15 condition significantly greater than the U_0 condition. No other significant differences between conditions were detected. On average, the S_0, the S_15, and the U_15 conditions had similar ratings, and, interestingly, the presence of nicotine alone in flavorless PG/VG liquid (U_15) appeared to be perceived just as sweet as the S_0 condition in this sample of dependent cigarette smokers (see Figure 12). Future research is needed to characterize the sensory experience and flavor attributes of nicotine alone in PG/VG only ECIG liquid solutions, and would benefit from examining how the sensory experience and perception of nicotine change as a result of dependence.

In the current study, sucralose did not reduce harshness ratings in the nicotine-containing ECIG condition, and the log-mean harshness scores were roughly identical on the GLMS (U_15 *M* = 1.57; S_15 *M* = 1.59). When participants were asked to describe the overall harshness/irritancy of the product, participants rated the U_15 and the S_15 conditions significantly greater than the OB condition, while the U_0 and the S_0 conditions ratings fell in the middle of the OB condition and the nicotine-containing ECIG conditions (see Figure 12). Participants' mean rating for describing the overall throat hit after using the nicotine-containing ECIG conditions was significantly greater than the mean rating after using the ECIG conditions without nicotine. A body of evidence has described that nicotine has a bitter taste (Carstens & Carstens, 2022; Mead et al., 2019; Pullicin et al., 2020), and flavors and sweeteners are used to make tobacco products more palatable by reducing the harshness that's associated with nicotine inhalation (Talhout et al., 2006). Although the current study did not find reductions in harshness ratings as a result of added sucralose, pervious research has found that adding sucralose to commercially-available, sweet-ECIG liquids was found to increase perceptions of sweetness and can also decrease ratings of harshness/irritation under certain conditions (Rosbrook et al., 2017). This study observed differences in sensory effects by the liquid-reservoir that was used, specifically, when taking puffs from a cartridge-fitted device; added sucralose increased sweetness ratings, but did not impact harshness/irritation ratings, similar to the current study. When taking puffs from a tank-fitted device, added sucralose decreased harshness/irritation ratings, but did not impact sweetness ratings (Rosbrook et al., 2017). This study suggests that similar to nicotine delivery (Hiler et al., 2020; DeVito & Krishnan-Sarin, 2018), the impact of sucralose on sensory experience may be a function of the combined influence of device characteristics, liquid constituents, and user behavior.

The current study did not reveal any significant differences between conditions on ratings of product liking of sweetness, harshness, and throat hit, however, prior research found that added sucralose did increase overall product liking (Kim et al., 2016; Rosbrook et al., 2017), and that sweet-flavored ECIGs receive greater product liking ratings than non-sweet-ECIG flavors (Goldenson et al., 2016; Kim et al., 2016). Assessment of participants' willingness to use the product again revealed that the ratings for the items "How likely would you be to use this product again if it was offered to you by a close friend?" and "How likely would you be to buy this product for personal use?" were significantly greater in the OB condition than all four ECIG conditions. Participants' ratings of "How likely would you be to use this product again if it was offered to you by a close friend?" revealed that the S_15 condition's mean rating was significantly greater than the U_15 condition's mean rating (Figure 13). Thus, sucralose appears to increase the likelihood of future product use in smokers. However, nicotine nor sucralose impacted participants' willingness to buy these products for personal use. Overall, the findings from the subjective effects items reported in this study indicate that OB cigarettes produced the greatest reinforcing effects than all four of the ECIG conditions indicating a higher abuse liability. Among the ECIG conditions, ECIG conditions that contained nicotine produced more pronounced drug effects and suppression of tobacco abstinence symptoms than the ECIG conditions without nicotine, and ECIG conditions that contained sucralose had more pronounced effects on product appeal than the unsweetened ECIG conditions.

Summary of Results

Overall, the OB condition had a higher abuse liability than the all four ECIG conditions. In terms of nicotine delivery, the OB condition delivered a larger dose of nicotine to participants, while the ECIG conditions that contained 15 mg/mL nicotine delivered lower doses of nicotine

on average. The U_15 condition was the only ECIG condition that delivered nicotine at concentrations that significantly differed from the U_0 and the S_0 conditions. This result influences many of the study findings as nicotine delivery drives the strength of the reinforcing effects observed in nicotine and tobacco products. Sucralose did not have any significant effects on nicotine delivery following a 10-puff, directed bout. However, additional research is needed to understand the impact that sucralose has on nicotine delivery following longer, *ad libitum* use. Participants took longer and larger puffs when using an ECIG that contained sucralose, therefore, differences in nicotine delivery may be observed following more puffs. Sweeteners may influence ECIG nicotine delivery, and thus ECIG abuse liability, by virtue of altering user behavior (i.e., puff topography). Results from the CPT revealed that OB cigarettes had a higher demand with few differences observed between the ECIG conditions. The results from this hypothetical purchase task suggests that these ECIG conditions would have a low likelihood of being purchased by smokers, even if these products were the only tobacco products on the market. Although, participants indicated they would consume ECIG puffs if they were offered free of charge. Participants worked significantly harder and earned more OB puffs during the PRT, however, the number of puffs earned in the U_0 condition and the S_15 condition did not significantly differ from the OB condition. Overwhelmingly, the OB condition produced greater subjective reinforcing effects resulting in more statistically significant subjective effects for OB than any of the ECIG conditions, specifically, OB was more reinforcing, more appealing, and reduced tobacco abstinence symptoms to a greater degree than the ECIG conditions. The ECIG conditions that contained nicotine produced more significant drug effects, such as dizziness, and reduced tobacco abstinence symptoms to a greater degree than the ECIG conditions without nicotine. Sucralose produced its greatest effects on measures of product appeal, such as “Did the

product taste good?", and on puff behavior as discussed above. OB cigarettes served as an effective positive control for this abuse liability assessment as they tested unequivocally positive on all of the outcome measures, and thus remains high on the abuse potential spectrum. In relation to OB cigarettes, every ECIG condition examined in the current study had a lower abuse liability than the OB condition. ECIG conditions that contained nicotine had an elevated abuse liability compared to ECIG conditions without nicotine and sucralose appeared to increase ECIG abuse liability by means of enhancing product appeal. In summary, the hypotheses for the current study were partially supported by the results described above; although the expected magnitude of effects for nicotine and sucralose manipulations were not observed.

Regulatory Implications

The Family Smoking Prevention and Tobacco Control Act (Public Law 111-31) granted the FDA the authority to regulate tobacco products in 2009, and extended the definition of 'tobacco product' to include ECIGs in 2016. The FDA intends to regulate ECIGs in order to protect the public health of those who use tobacco products and those who do not. FDA regulation therefore must address the balance between the potential public health benefits of ECIGs for smokers as a smoking alternative or cessation tool, and the potential public health harms for youth and nicotine-naïve individuals who are attracted to ECIGs via marketing and then continue to use them due to their reinforcing effects and capacity to engender nicotine dependence. Combustible cigarettes have a high abuse liability as determined by this study and many others (Campbell et al., 2022; Cobb et al., 2019; Maloney et al., 2019; Maloney et al., 2021; Rensch et al., 2021; Stiles et al., 2017; West et al., 2000), largely due to their unmatched rate of nicotine delivery. ECIGs have been found to have a lower abuse liability than cigarettes in cigarette smokers, but still carry elevated rates of abuse liability compared to traditional forms

of NRT (Stiles et al., 2017; Maloney et al., 2019). The importance of nicotine delivery in ECIG abuse liability has been demonstrated in multiple studies (Bullen et al., 2010; Hiler et al., 2017; Maloney et al., 2019; Perkins et al., 2017), including the current study. National sales data showing that zero-nicotine ECIG products accounted for less than 1% of the dollar market value share across 2013-2018 (Romberg et al., 2019) illustrates the importance of nicotine in ECIG abuse liability.

The availability of flavors, particularly sweet flavors, are a leading reason for ECIG use (Soneji et al., 2019). Appetitive flavors in sweet-flavored ECIGs exploit chemical-specific, flavor-sensory cues used by beverage and candy manufacturers (Brown et al., 2014). The repeated pairing of sweeteners and flavors with nicotine can create a collection of associative sensory cues and rewards through Pavlovian conditioning (Budworth, 2019). Sensory cues, such as perceived sweetness, have intrinsically motivating and naturally rewarding effects and could lead to stronger sensory cues (Budworth, 2019), and potentially could entangle the neural networks and the reward systems involved in nicotine and sugar addiction. Adding sweeteners to non-sweet-ECIG liquids has been found to increase brain responses to ECIGs (Kroemer et al., 2018). Smokers who switched to ECIGs using tobacco flavors were increasingly likely to migrate away from tobacco flavors to non-tobacco flavors over time (Russell et al., 2018). This observation may suggest that sweet-ECIG flavors may be initiating and creating stronger ECIG dependence instead of being a tool for facilitating smoking cessation in smokers. Although smokers often report flavor availability as an important factor for aiding smoking cessation in observational studies (Goldenson et al., 2019; Soule et al., 2016), results from a randomized clinical study that asked cigarette smokers to abstain from smoking and instead switch to use either a sweet-flavored ECIG or unflavored (no flavor) nicotine-containing ECIG suggests this

may not be true. Results from this study did not find an effect of flavor on smoking lapses during the study, enjoyment of the ECIG, ease of transitioning from smoking, or motivations to quit smoking (Dyer et al., 2021). Thus, these anecdotal reports of sweet-ECIG flavor importance in smoking cessation may be a reflection of ECIG use expectancies and not representative of real-life behaviors. After all, ECIG cessation trials have not yielded quit rates beyond those seen with traditional forms of NRT and is likely due to lack of nicotine delivery (Maloney et al., 2021), not lack of flavor variety. Systematic evaluations of ECIGs and their components, like in the current study, can inform policies and product standards aimed at reducing the rapid initiation and growing popularity of ECIGs among youth, young adults, and never-smoking adults. Youth cite flavors as a primary reason for ECIG initiation (Alexander et al., 2019; Landry et al., 2019), and fruit and candy flavors are the most popular flavors among youth (Soneji et al., 2019). Furthermore, flavored ECIG use is associated with higher odds of initiating (Dai & Hao, 2016) and progressing to cigarette use (Primack et al., 2015). These data, paired with the current study that demonstrates that sucralose elevates product appeal to increases ECIG abuse liability, but has minimal effects on reducing tobacco and nicotine abstinence symptoms, suggests that sucralose, and possibly all sweeteners, would be an important regulatory target in the interest of maximizing potential ECIG public health benefit. This regulation would be a justifiable policy as sweeteners are not GRAS for inhalation (Sears et al., 2017). This ban may have unintended consequences in that it may facilitate black market purchasing of sweeteners or sweet-flavored ECIG products (Freitas-Lemos et al., 2021), or prompt increases in do-it-yourself (DIY) ECIG liquid solution creations (Balewska & Raciborski, 2021; Guy et al., 2019). However, the potential reduction in initiation rates stands to have a large impact on public health.

Limitations

This study had several notable limitations that should be considered when interpreting the results. A major limitation of this study was the impacts of COVID-19 and recruitment issues and the final sample size. Power analyses determined that this study would need a sample size of 30 participants to detect effects of sucralose and nicotine. A sample size of 30 would have provided this study more power to detect smaller effects that sucralose may have had on these abuse liability measures. Therefore, this study was under powered to detect effects on many of these outcome measures, and therefore is limited in its generalizability. Despite the small sample size, this study had adequate power to detect robust effects, and was able to provide an informative initial understanding of the impacts of sucralose on ECIG abuse liability in cigarette smokers. Another limitation and possible reason for lower than predicted impacts of sucralose is the choice of ECIG device used. Previous research has shown that the impacts of sucralose on perceptions of sweetness and harshness are impacted by the device being used to aerosolize the ECIG liquid solutions, specifically the type of liquid reservoir (Rosbrook et al., 2017), thus the effect of the sucralose manipulation in the current study may have been attenuated by administering the sweetener via a tank-fitted device. While considerations for device and liquid features were taken into account to maximize likelihood of nicotine delivery, similar considerations regarding sucralose should be made in future research. The sucralose concentration that was chosen for this study was intended to be representative of the average sucralose levels in the ECIG liquid solutions produced by the manufacturer from where the study ECIG liquids were purchased. This study may have benefited from selecting a sweetener concentration that was representative of “very” sweet flavors, such as popular candy, dessert, and fruit flavors may have resulted in greater measurable effects, however, doing so would have

limited the generalizability of the study as many non-sweet-flavored ECIGs also contain sweeteners (Fagan et al., 2018; Miao et al., 2016).

Another limitation that should be noted is the varying degrees of nicotine exposure and satiation following the 10-puff, directed bout and the impact nicotine exposure and delivery may have had on subsequent responding on the PRT. Previous studies using the PRT to investigate ECIGs administered fixed- and progressive-ratio tasks following periods of tobacco and nicotine abstinence (Audrain-McGovern et al., 2016; Copp et al., 2015) or provided a small sample of puffs after a period of abstinence (i.e., two puffs as in Hoetger et al., 2021), minimizing results being confounded from variable nicotine exposure at the start of the task. While the current study would have also benefited from administering the PRT after periods of extended nicotine and tobacco abstinence, this study is strengthened by the study's systematic measurement of nicotine delivery across conditions, which would not have been possible if we measured nicotine delivery pre- and post-PRT or feasible with additional sessions. Another major limitation of this study, and other ECIG studies, is the difficulty of finding an ECIG device and liquid combination capable of delivering cigarette-like nicotine delivery to cigarette smokers. Because the majority of the rewarding properties of cigarettes and ECIGs stems from nicotine delivery, future abuse liability assessments that have matched nicotine delivery across ECIG products and OB cigarettes would provide valuable information on ECIG abuse liability.

This study has several limitations in regards to the purchase tasks, first, the likelihood of participant fatigue while responding to two, back-to-back purchase tasks with small incremental increases in price and 25 price points may have impacted the quality of participants' responding on these tasks. Additionally, the CPT daily expenditures (O_{max}) for the ECIG products in this study were lower than seen in previous studies (Barnes et al., 2017), this could be due to

historical effects of the study taking place during COVID-19 (data collected from February 2020 to December 2021). COVID-19 had a significant impact on many individuals' financial wellbeing, in addition to individuals' health. In the current study, 64% of participants were unemployed at the time of participation. Hardships brought on during COVID-19 should be taken into consideration when interpreting this data. Overall, despite these limitations, this study provides a useful, systematic, initial understanding of the impact of ECIG sweeteners on ECIG abuse liability across a variety of measures (physiological, subjective, and behavioral).

Conclusions

This within-subject, clinical laboratory study investigated the effects of sucralose alone and paired with 15 mg/mL nicotine on nicotine delivery, puff-behavior, a self-administration task, measures of product demand, and subjective effects measures. Overall, the results from this study demonstrated that OB cigarettes had a higher abuse liability than the ECIG conditions examined, irrespective of nicotine or sucralose content, on nearly all measures of abuse liability. In respect to the ECIG conditions, nicotine had a greater impact on ECIG abuse liability than sucralose. The nicotine-containing ECIG conditions produced the greatest effects on nicotine delivery and suppression of tobacco abstinence symptoms. Sucralose increased abuse liability primarily through measures of product appeal and puffing behavior. This study adds support to prior research demonstrating the role of nicotine in ECIG abuse liability (Bullen et al., 2010; Hiler et al., 2017; Maloney et al., 2019; Perkins et al., 2017). This study adds new evidence to the ECIG literature that added sucralose can increase ECIG abuse liability by means of increasing product appeal, while having little impacts on abuse liability as measured by tobacco abstinence symptom suppression, potentially making sucralose, and possibly other sweeteners, a

potential target for regulation aimed at protecting the health of nicotine-naive individuals who are drawn to ECIGs by aggressive industry marketing.

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APPENDIX A

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: Effects of Electronic Cigarette Liquid Characteristics in Cigarette Smokers

VCU INVESTIGATOR: Thomas Eissenberg, PhD, Professor of Psychology, (804) 827-3562

SPONSOR: National Institutes of Health/National Institute of Drug Abuse/ Food and Drug Administration

ABOUT THIS CONSENT FORM

You are being invited to participate in a research study. **It is important that you carefully think about whether being in this study is right for you and your situation.**

This consent form is meant to assist you in thinking about whether or not you want to be in this study. **Please ask the investigator or the study staff to explain any information in this consent document that is not clear to you.** You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Your participation is voluntary. You may decide to not participate in this study. If you do participate, you may withdraw from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

AN OVERVIEW OF THE STUDY AND KEY INFORMATION

The purpose of this research study is to learn about how different electronic cigarette liquid characteristics, such as nicotine and sweeteners affect the vaping experience (how you feel), user behavior (how you puff), blood nicotine levels, your willingness to hypothetically pay for the product, and work for puffs of the product (by pressing a button on a keyboard).

The results of this study will be used to help us better understand how electronic cigarette liquid characteristics, like nicotine and sweeteners, affect a smokers experience with the product. Specifically, how it feels to use the product, puffing behaviors, willingness to use the product again, and blood nicotine levels.

In this study, you will be asked to do the following things:

1. Due to COVID-19, you will be required to have your temperature checked and answer questions related to COVID-19 symptoms and exposure prior to each in-person session. Upon arriving to the study site location, you will be required to wear a mask in the building at all times (except during smoking and vaping in the lab).
2. During study visits, we will use an intercom system (i.e., zoom) on the computer to communicate with you while you are in the session room. We have the ability to turn on the camera to facilitate communication, but will not use this feature unless requested or

for troubleshooting reasons. This communication between participants and researchers will not be recorded or used for research purposes.

3. During this first visit, you will answer questionnaires to confirm your eligibility for this study and be asked to present a valid form of ID to confirm you're of legal age. Women will take a urine pregnancy test. If you are found to be ineligible for the study, your participation will end.
4. If found eligible, we will ask you to visit the Center for the Study of Tobacco Products Laboratory for 5 approximately 3.5-hour study visits that must be separated by at least 48 hours, and will not occur more than 2 times per week.
5. Before each visit, abstain from all tobacco products for at least 12 hours. In addition, the use of any other nicotine-containing products (like e-cigarettes, nicotine gum or the nicotine patch) is prohibited. We will ask you to take a simple breath test to make sure that you have complied with these restrictions. Our tests are not perfect, but they are the only measures that we can accept to make certain that you have complied with the no tobacco/no nicotine restrictions.
6. We will also ask you to abstain from caffeinated beverages for 1 hour before each session.
7. We will also measure your blood pressure (with a blood pressure cuff on your arm) to make sure it is in a safe range to participate.
8. During the study sessions, we will ask you to turn off your cell phone for the duration of the session.
9. Each session will begin with a series of questions that asks about any changes in health you may have experienced since your last study visit. Then there will be a one hour waiting period during which we will have you sit in the session room to allow you to get comfortable and used to the setting. During this waiting period you will not be allowed to use your phone, however, we will provide you with a movie to watch or magazine to read.
10. After this 1-hr waiting period, a phlebotomist or nurse will take a blood sample prior to and immediately after a 10-puff session product bout. Because this study only requires two blood draws per session, a butterfly needle will be used to sample blood as it is a smaller needle and less invasive than an indwelling catheter. During each session we will take approximately 7 mL of blood or approximately 1.5 teaspoons each blood draw for a total of 14 mL or 3 teaspoons of blood drawn per session. Throughout your participation in this study, we will take approximately 70 mL of blood total, approximately 4 to 5 tablespoons. . Inserting a needle to sample blood can be challenging for some individuals with who have more restricted venous access (e.g., small veins, rolling veins). In this laboratory we will attempt to insert a butterfly needle for blood sampling no more than three times per sample and, if all three attempts are unsuccessful, we will discontinue the session and pay you for the time that you spent complying with study conditions before the session began ($15) and also for the time you spent in the laboratory ($15/hour).
11. During each session, we will also monitor your heart rate (with a device that attaches to your finger) and ask you to respond to several questionnaires to measure how you feel before and after you use the session specific study product.
12. In each session, you will receive one of the five study products: a cigarette of your own brand (that we purchase for you to use in the session), or an electronic cigarette filled with 1 of 4 different investigational study e-liquids/e-juices. Some of the liquids contain nicotine.

During each session you will not know which liquid was used to fill the electronic cigarette. This is called blinding, and it is done so that a fair evaluation of results may be made. During the session we will ask you to use the study product we provide at two separate times. The first time, we will ask you to take only 10 puffs, and we will tell you when to take each of these puffs. The second time we will ask you to do a task in which you press a button on a computer keyboard to earn puffs. You can earn up to as many puffs as you would like to take, but the button presses required to earn a puff increases each time you earn a puff. At each of these two times we need you to remain seated in a comfortable chair while you are using the study product.

13. When you use the e-cigarette, you may notice that it is connected to a computer and that there are pieces of equipment attached to the study product. The computer and this equipment are measuring how you are using the product (the size and number of the puffs that you take).
14. There may be rare instances in which the equipment we use malfunctions during a session. If this happens, we may stop the session and ask you to return on another day to repeat that session. In these instances, if the equipment malfunctions in the first half of the session, we will pay you half of the money you would have earned in that session. If the equipment malfunction occurs in the second half of the session, we will pay you the full amount for that session.
15. In each session we will also ask you to complete a computerized task that asks you how much you would hypothetically pay for a day's worth of personal use of the session product at increasing prices.

The total time for your participation in this study will last up to 17.5 hours. Approximately 30 individuals will participate in this study.

This study will not use your samples to sequence all or part of your DNA.

WHAT ALTERNATIVES ARE AVAILABLE?

This is not a therapeutic study. You have the alternative not to participate. If you do not feel comfortable answering questions on the computer, paper forms are available.

WHAT RISKS AND DISCOMFORTS COULD I EXPERIENCE FROM BEING IN THE STUDY?

There are both risks and benefits of participating in research studies.

Most Common Risks and Discomforts	Benefits to You and Others
1. You may experience some discomfort during abstinence from cigarettes and nicotine before the session or while using electronic cigarettes during the session. Side effects from using	This is not a treatment study, and you are not expected to receive

products that contain nicotine can include sweating, lightheadedness, dizziness, nausea, and nervousness. These effects are less likely in individuals who use nicotine-containing products regularly. Side effects from tobacco/nicotine abstinence can include irritability, anxiety, restlessness, excessive hunger, difficulty concentrating, and sleep disturbance. These are common abstinence symptoms in cigarette smokers. Though uncomfortable, these feelings are not medically dangerous. 2. Some people who use e-cigarettes have reported experiencing seizures. Some of these individuals reported a prior history of seizures or using other substances at the same time as their e-cigarette. 3. In some cases e-cigarette use has led to respiratory/pulmonary illnesses such as difficulties breathing, shortness of breath, cough, and/or chest pain before hospitalization. In rare cases, e-cigarette use has led to death. In some cases symptoms of mild to moderate gastrointestinal illness such as nausea, abdominal pain, vomiting, diarrhea, or fevers or fatigue have been reported. The Centers for Disease Control and Prevention advises that e-cigarette, or vaping products should never be used by youth, young adults, or women who are pregnant. Adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products. If you use e-cigarette products, monitor yourself for all of these symptoms and promptly seek medical attention if you have concerns about your health. 4. Electronic cigarettes have be known to overheat and exploded. Although we use new device equipment and check for inconsistences before every use, there is a risk of minor or major burn injuries or inhalation injuries from the use of e-cigarettes. 5. The e-cigarette liquid that we give you may contain more nicotine than you usually use and may have unknown risks, although many e-cigarette users report using these liquids. Inform the study staff immediately if you experience any discomfort from using the electronic cigarette. 6. On very rare occasions, you may experience small droplets of liquid during inhalation of the electronic cigarette we provide. You may find these droplets to be unexpected and/or unpleasant. This experience has been reported by electronic cigarette users, and they report that it is an annoyance that does not appear to present any medical danger. If this occurs, we will immediately replace the electronic cigarette device you are using. 7. You may also feel some discomfort when the nurse/phlebotomist inserts or withdraws the needle when blood samples are taken. We try very hard to minimize your discomfort at these times, and	any direct medical benefits from your participation in the study. The information from this research study may lead to a better understanding of e-cigarettes.

the use of a trained nurse/phlebotomist and sterile, disposable equipment enhances comfort while reducing the risk of bruising and infection. 8. Your heart rate and blood pressure may increase; if either increases above acceptable limits, your participation may be stopped for your safety. 9. You may find the monitoring equipment uncomfortable. 10. The researchers will let you know about any significant new findings (such as additional risks or discomforts) that might make you change your mind about participating in the study. 11. The use of e-cigarettes involves risks that are currently unknown or unforeseeable. Using e-cigarettes may involve risks to a developing embryo or fetus that are currently unknown. Please contact study staff if you experience any adverse events following participation in the study sessions. **Non-Physical Risks:** 12. Participation in research might involve some loss of privacy. There is a small risk that someone outside the study could see and misuse information about you. 13. The study questionnaires ask personal questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable.	

In general, we will not give you any individual results from the study.

Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask the study staff.

WILL I BE PAID TO PARTICIPATE IN THE STUDY?

You will be paid $30 for completing the initial screening visit. You will be paid for the time that you are not using tobacco prior to session and for your time in the laboratory: you will receive $80 after the first session, $100 after the second, third, and fourth session, and $150 after the fifth session. In all, you can earn $560 for completing this study. All payments will be in cash. You will also be reimbursed parking up to $8 for each of the five study sessions.

Total payments within one calendar year that exceed $600 will require the University to annually report these payments to the IRS and you. This may require you to claim the compensation you receive for participation in this study as taxable income. VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THE STUDY?

If you are injured by, or become ill, from participating in this study, please contact the research nurse immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Dr. Lipato, your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness, it is very important to follow all study directions.

CAN I STOP BEING IN THE STUDY?

You can stop being in this research study at any time. Leaving the study will not affect your medical care, employment status, or academic standing at VCU or VCU Health. Tell the study staff if you are thinking about stopping or decide to stop.

If you leave the study before the final regularly scheduled visit, you will be able to keep any money that you earned in the study up to that point.

Your participation in this study may be stopped at any time by the investigator without your consent. The reasons might include:

- the investigator thinks it necessary for your health or safety
- you are found to not be eligible for the study
- the sponsor has stopped the study
- you have not followed study instructions
- administrative reasons require your withdrawal

HOW WILL INFORMATION ABOUT ME BE PROTECTED?

VCU has established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your information may be kept in these databases but are only accessible to individuals working on this study or authorized individuals who have access for specific research related tasks.

Identifiable information in these databases are not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed.

Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring and overseeing this study:

- The study Sponsor, representatives of the sponsor and other collaborating organizations
- Representatives of VCU and the VCU Health System
- Officials of the Department of Health and Human Services

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time. In the future, identifiers might be removed from the information and samples you provide in this study, and after that removal, the information/samples could be used for other research studies by this study team or another researcher without asking you for additional consent.

There are no plans to share any money or profits with you if the use of your sample(s) results in inventions or discoveries that have commercial value.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

WHO SHOULD I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

If you have any questions, complaints, or concerns about your participation in this research, contact:

Dr. Alison Breland or Dr. Thomas Eissenberg at (804) 827-3562 or at abbrelan@vcu.edu or teissenb@vcu.edu

The medically responsible investigator is Dr. Thokozeni Lipato (thokozeni.lipato@vcuhealth.org).

The researcher/study staff named above is the best person(s) to call for questions about your participation in this study.

If you have general questions about your rights as a participant in this or any other research, you may contact:

Virginia Commonwealth University Office of Research

800 East Leigh Street, Suite 3000

Box 980568

Richmond, VA 23298

Telephone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

STATEMENT OF CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form for my records.

Signature Block for Enrolling Adult Participants	
_____ Adult Participant Name (Printed)	
_____ Adult Participant's Signature	_____ Date
_____ Name of Person Conducting Consent Discussion (Printed)	
_____ Signature of Person Conducting Consent Discussion	_____ Date
_____ Principal Investigator Signature (if different from above)	_____ Date

APPENDIX B

ECIG Cigarette Purchase Task (CPT)

E-Cigarette Purchase Task

1. Imagine a TYPICAL DAY during which you smoke. The following questions ask how many times you would take 10 puffs of the ECIG you sampled today if every 10 puffs cost various amounts of money.
2. The only available e-cigarette is the one you just sampled. Assume that you have the same income/savings that you have now and NO ACCESS to any of your own-brand cigarettes or nicotine products other than e-cigarette offered at these prices.
3. In addition, assume that you would consume the puffs of the e-cigarette that you request on that day; that is, you cannot save or stockpile e-cigarette puffs for a later date. Please respond to these questions honestly.

How many times would you take 10 puffs of the ECIG you sampled today if they were ____each at the following prices?

Number of times you would take 10 puffs of the ECIG you tried today?	**Price per 10 puffs of the ECIG you tried today.**
	$0 (free)
	$0.01 per 10 puffs?
	$0.02 per 10 puffs?
	$0.05 per 10 puffs?
	$0.10 per 10 puffs?
	$0.15 per 10 puffs?
	$0.20 per 10 puffs?
	$0.25 per 10 puffs?
	$0.30 per 10 puffs?
	$0.35 per 10 puffs?
	$0.40 per 10 puffs?
	$0.45 per 10 puffs?
	$0.50 per 10 puffs?
	$0.60 per 10 puffs?
	$0.70 per 10 puffs?
	$0.80 per 10 puffs?
	$0.90 per 10 puffs?
	$1.00 per 10 puffs?
	$2.00 per 10 puffs?
	$3.00 per 10 puffs?
	$4.00 per 10 puffs?
	$5.00 per 10 puffs?
	$10.00 per 10 puffs?
	$15.00 per 10 puffs?
	$20.00 per 10 puffs?

Cigarette Purchase Task (CPT)

Own-Brand Cigarette Purchase Task

1. Imagine a TYPICAL DAY during which you smoke. The following questions ask how many times you would take 10 puffs of your own-brand of cigarettes (roughly equivalent to 1 cigarette) if they cost various amounts of money.
2. The available cigarettes are your own-brand. Assume that you have the same income/savings that you have now and NO ACCESS to any cigarettes or nicotine products other than those offered at these prices.
3. In addition, assume that you would consume the cigarettes that you request on that day; that is, you cannot save or stockpile cigarettes for a later date. Please respond to these questions honestly.

How many times would you take 10 puffs (smoke ~1 cigarette) if your own-brand of cigarettes if they were ____each at the following prices?

Number of times you would smoke 10 puffs (~1 cigarette) of your own-brand of cigarettes	**Price per 10 puffs (~ 1 cigarette) of your-own brand of cigarettes**
	$0 (free)
	$0.01 each?
	$0.02 each?
	$0.05 each?
	$0.10 each?
	$0.15 each?
	$0.20 each?
	$0.25 each?
	$0.30 each?
	$0.35 each?
	$0.40 each?
	$0.45 each?
	$0.50 each?
	$0.60 each?
	$0.70 each?
	$0.80 each?
	$0.90 each?
	$1.00 each?
	$2.00 each?
	$3.00 each?
	$4.00 each?
	$5.00 each?
	$10.00 each?
	$15.00 each?
	$20.00 each?

APPENDIX C

Cross-Price Cigarette Purchase Task (CP-CPT)

Cross-price Own Brand Cigarette Purchase / Session Specific E-cigarette Task

- Now imagine another TYPICAL DAY during which you use cigarettes or e-cigarettes.
- The following questions ask how many times you would buy 10 puffs of your own brand cigarettes and 10 puffs of the session specific e-cigarettes if your own brand cigarettes cost various amounts of money but the price of the session specific e-cigarette stayed the same.
- The only available cigarettes are your own brand and the only available e-cigarettes are this session's product.
- Assume that you have the same income/savings that you have now and NO ACCESS to any cigarettes, e-cigarettes, or nicotine products other than those offered at these prices.
- In addition, assume that you would consume the puffs that you request on that day; that is, you cannot save or stockpile puffs for a later date.
- Please respond to these questions honestly.

[Please note the following two sentences will be displayed for each of the **X1/X2** prices below. Participants will continue on this task until either they make purchases at all of the prices, or they elect to purchase zero on two successive prices. Several equations are hidden to perform the calculations needed to display the totals.]

-If 10 puffs of your own brand cigarettes cost **X1** and 10 puffs of the session specific e-cigarettes cost **X2**:

- How many **times** would you buy 10 puffs of your own brand cigarettes to consume in one day?

-How many **times** would you buy 10 puffs of the session specific e-cigarettes to consume in one day?

- You would buy 10 puffs of your own brand cigarettes **Y1 times** for **$Z1** and 10 puffs of the session specific e-cigarettes **Y2 times** for **$Z2** for a total of **$Z3**.

Y1 times you would buy 10 puffs of your own brand cigarettes (numeric response by participant)	*X1 (cigarette price)*	*Y2 times you would buy 10 puffs of the session specific e-cigarettes (numeric response by participant)*	*X2 (e-cigarette price)*
	$0 (free)		$1.00
	$0.01		$1.00
	$0.02		$1.00
	$0.05		$1.00
	$0.10		$1.00
	$0.15		$1.00
	$0.20		$1.00
	$0.25		$1.00
	$0.30		$1.00
	$0.35		$1.00
	$0.40		$1.00
	$0.45		$1.00
	$0.50		$1.00
	$0.60		$1.00
	$0.70		$1.00
	$0.80		$1.00
	$0.90		$1.00
	$1.00		$1.00
	$2.00		$1.00
	$3.00		$1.00
	$4.00		$1.00
	$5.00		$1.00
	$10.00		$1.00
	$15.00		$1.00
	$20.00		$1.00

APPENDIX D

Hughes-Hatsukami Withdrawal VAS Scale (Hughes & Hatsukami, 1986).

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

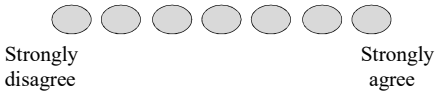
	Not at all	**Extremely**
1. URGES to smoke		
2. Irritability/frustration/anger		
3. Anxious		
4. Difficulty concentrating		
5. Restlessness		
6. Hunger		
7. Impatient		
8. CRAVING a cigarette/nicotine		
9. Drowsiness		
10. Depression/feeling blue		
11. Desire for sweets		

APPENDIX E

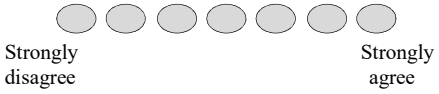
Tiffany-Drobes Questionnaire of Smoking Urges-Brief (QSU; Cox, Tiffany, & Christen, 2001)

For each item, please indicate how you feel RIGHT NOW

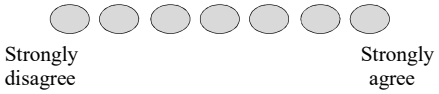
I have a desire for a cigarette right now.



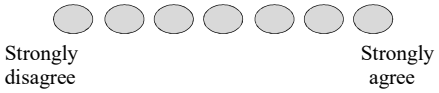
Nothing would be better than smoking a cigarette right now.



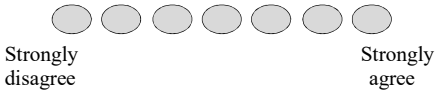
If it were possible, I probably would smoke now.



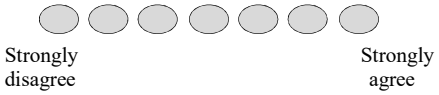
I could control things better right now if I could smoke.



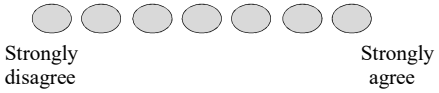
All I want right now is a cigarette



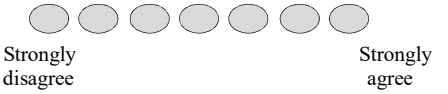
I have an urge for a cigarette.



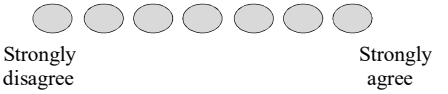
A cigarette would taste good now.



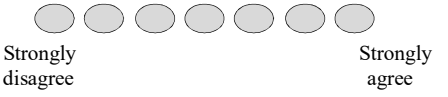
I would do almost anything for a cigarette now.



Smoking would make me less depressed.



I am going to smoke as soon as possible.



APPENDIX F

Positive and Negative Affect Schedule (PANAS)

(Watson, Clark, & Tellegen, 1988).

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way right now, that is, at this present moment. Use the following scale to record your answers.

very slightly or not at all	A little	moderately	quite a bit	extremely

1. interested
2. distressed
3. excited
4. upset
5. strong
6. guilty
7. scared
8. hostile
9. enthusiastic
10. proud
11. irritable
12. alert
13. ashamed
14. inspired
15. nervous
16. determined
17. attentive
18. jittery
19. active
20. afraid

APPENDIX G

Cigarette Evaluation Questionnaire (CEQ; Cappelleri et al., 2007)

Please mark the number that best represents how smoking made you feel (1–not at all, 2–very little, 3–a little, 4–moderately, 5–a lot, 6–quite a lot, 7–extremely).

1. Was the product satisfying?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

2. Did the product taste good?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

3. Did you enjoy the sensations in your throat and chest?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

4. Did using the product calm you down?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

5. Did using the product make you feel more awake?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

6. Did using the product make you feel less irritable?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

7. Did using the product help you concentrate?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

8. Did using the product reduce your hunger for food?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

9. Did using the product make you dizzy?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately
   5 [ ] A lot
   6 [ ] Quite a lot
   7 [ ] Extremely

10. Did using the product make you nauseous?
   1 [ ] Not at all
   2 [ ] Very little
   3 [ ] A little
   4 [ ] Moderately

5 [ ] A lot
6 [ ] Quite a lot
7 [ ] Extremely

11. Did using the product immediately relieve your craving for a cigarette?
1 [ ] Not at all
2 [ ] Very little
3 [ ] A little
4 [ ] Moderately
5 [ ] A lot
6 [ ] Quite a lot
7 [ ] Extremely

12. Did you enjoy using the product?
1 [ ] Not at all
2 [ ] Very little
3 [ ] A little
4 [ ] Moderately
5 [ ] A lot
6 [ ] Quite a lot
7 [ ] Extremely

APPENDIX H

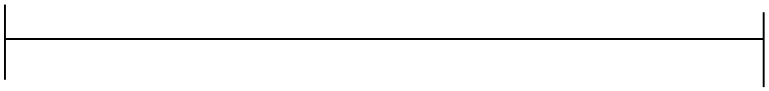
Drug Effects Questionnaire (DEQ; de Wit & Phillips, 2012)

You will be asked to indicate your answers to the following questions about the drug you consumed by marking on the line to indicate how much the adjective or description applies to you. Please indicate how you are feeling **right now**.

NOT AT ALL EXTREMELY

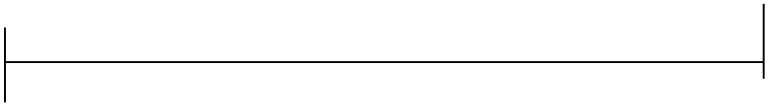
1. Do you FEEL a drug effect right now?

NOT AT ALL EXTREMELY



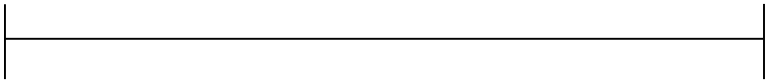
2. Do you LIKE any of the effects you are feeling right now?

NOT AT ALL EXTREMELY



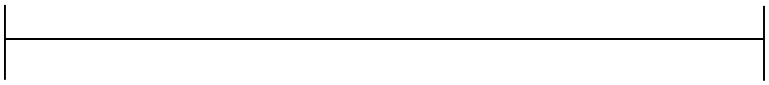
3. Do you DISLIKE any of the effects you are feeling right now?

NOT AT ALL EXTREMELY



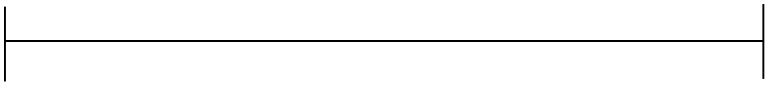
4. Are you buzzed right now?

NOT AT ALL EXTREMELY



5. Would you like MORE of the product you used, right now?

NOT AT ALL EXTREMELY



APPENDIX I

Direct Effects of Nicotine (DEN) scale (Perkins et al., 1994)

Direct Effects of Nicotine Scale

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

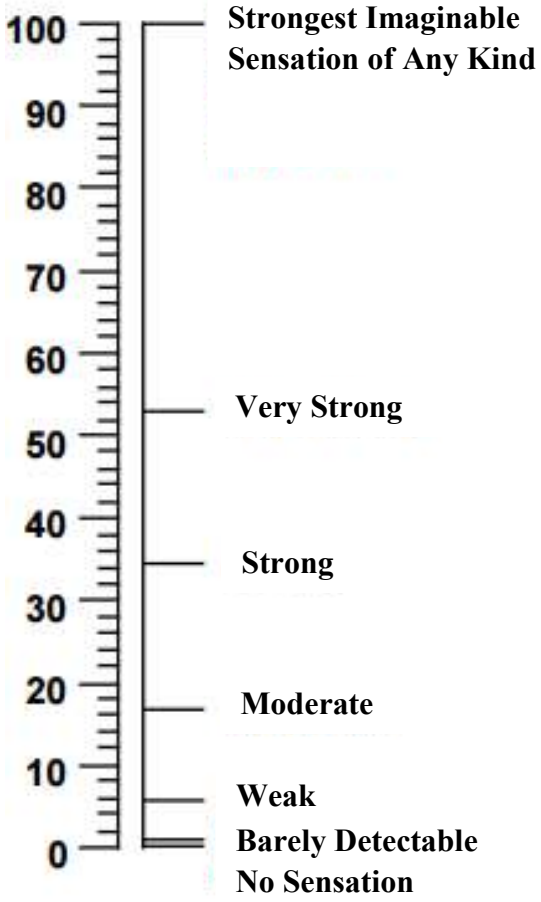
	Not at all	**Extremely**
1. Nauseous		
2. Dizzy		
3. Lightheaded		
4. Nervous		
5. Sweaty		
6. Headache		
7. Excessive salivation		
8. Heart pounding		
9. Confused		
10. Weak		

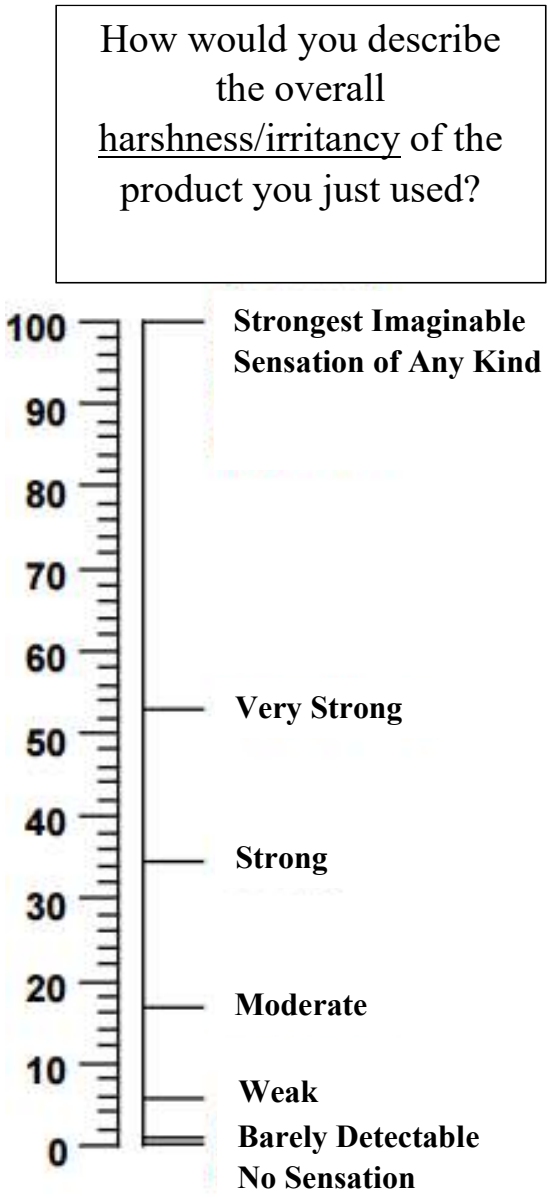
APPENDIX J

General Labeled Magnitude Scale (gLMS; Green, Shaffer, & Gilmore, 1993)

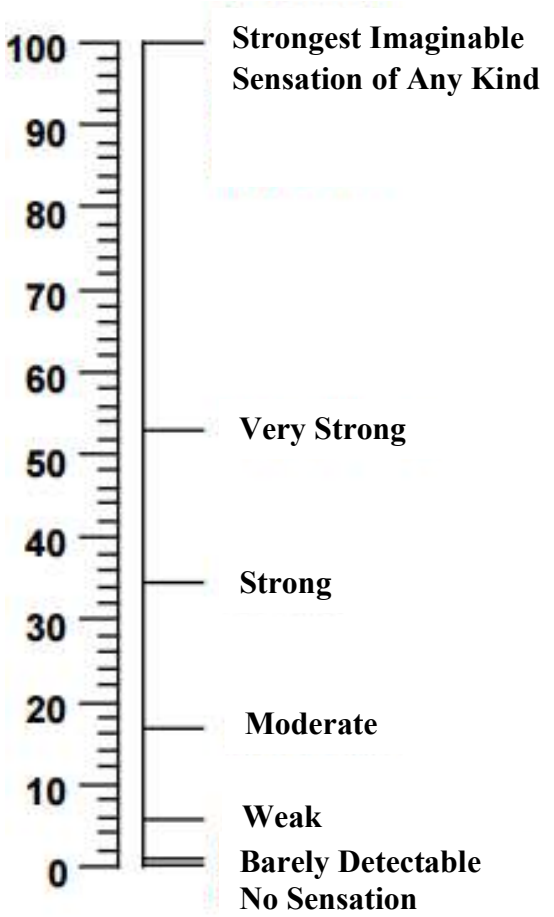
For each item, please indicate how you would describe the ECIG you just used by placing a mark on the vertical numbered line.

How would you describe the overall sweetness of the product you just used?



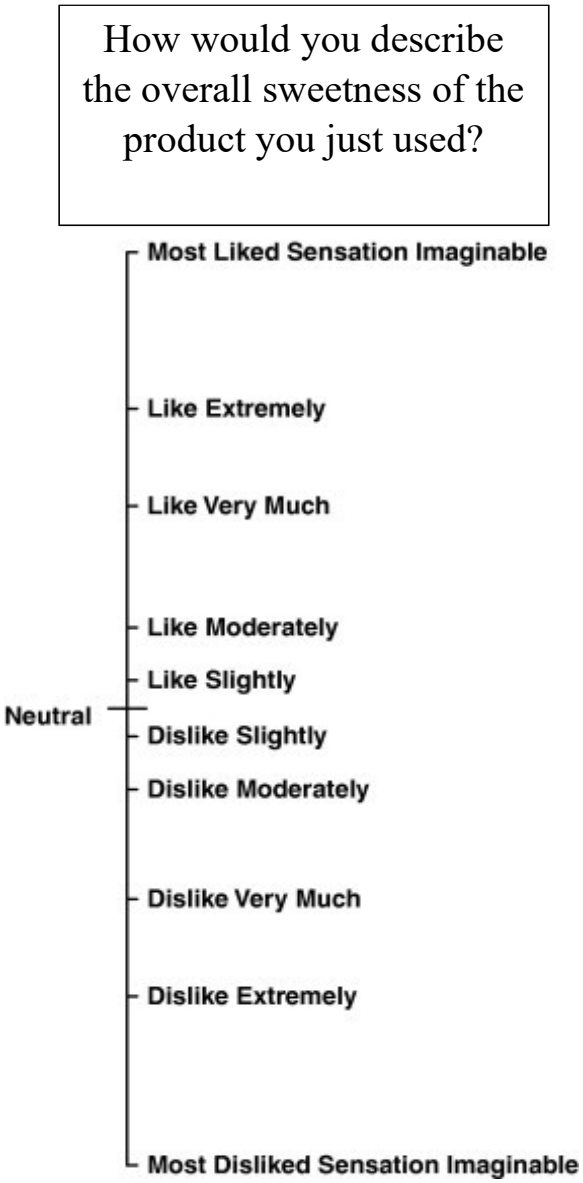

How would you describe the overall harshness/irritancy of the product you just used?
100
90
80
70
60
50
40
30
20
10
0
Strongest Imaginable Sensation of Any Kind
Very Strong
Strong
Moderate
Weak
Barely Detectable
No Sensation

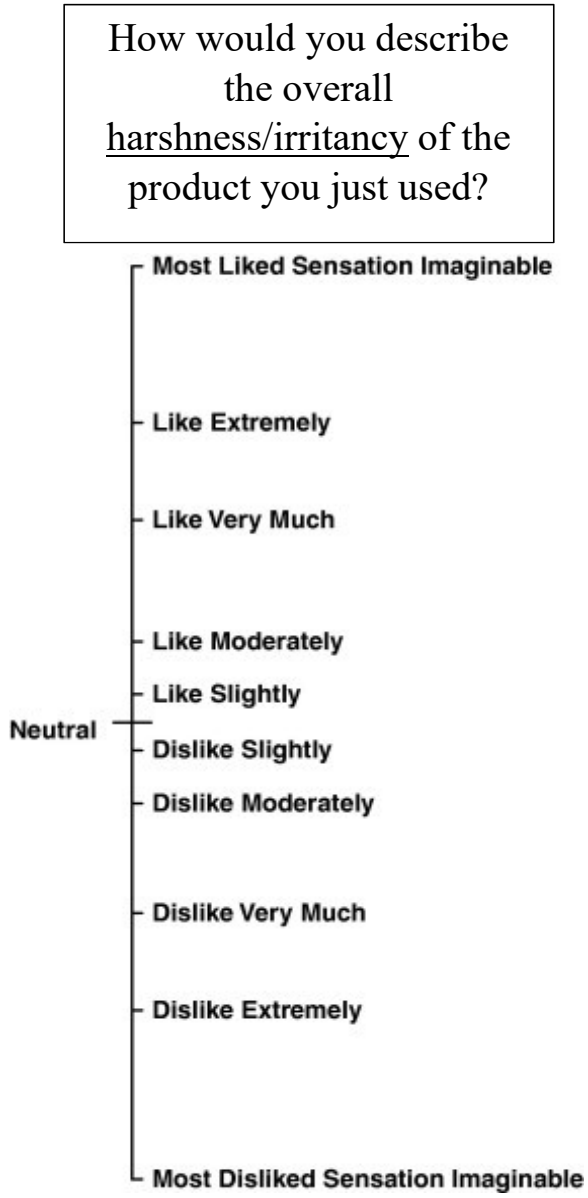
How would you describe the <u>throat hit</u> of the product you just used?

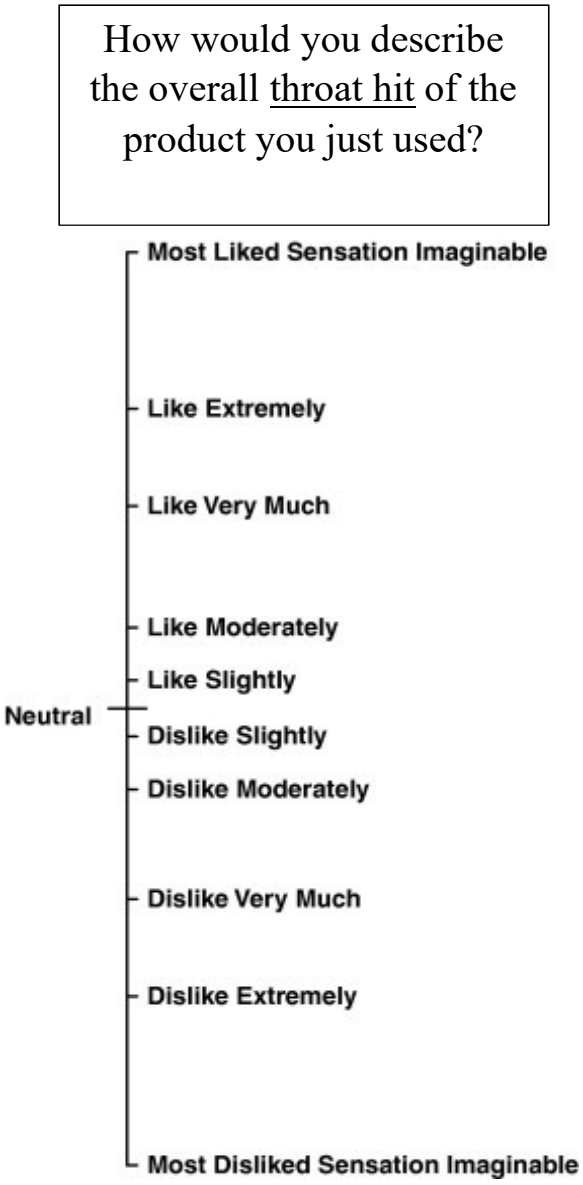


APPENDIX K

Labeled Hedonic Scale (LHS; Lim, Wood, & Green, 2009)




How would you describe the overall harshness/irritancy of the product you just used?
Most Liked Sensation Imaginable
Like Extremely
Like Very Much
Like Moderately
Like Slightly
Neutral
Dislike Slightly
Dislike Moderately
Dislike Very Much
Dislike Extremely
Most Disliked Sensation Imaginable

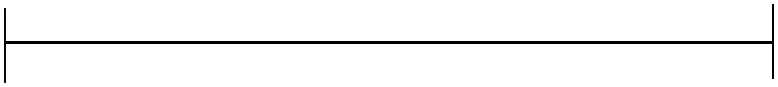

How would you describe the overall throat hit of the product you just used?
Most Liked Sensation Imaginable
Like Extremely
Like Very Much
Like Moderately
Like Slightly
Neutral
Dislike Slightly
Dislike Moderately
Dislike Very Much
Dislike Extremely
Most Disliked Sensation Imaginable

APPENDIX L

Willingness to use again questionnaire

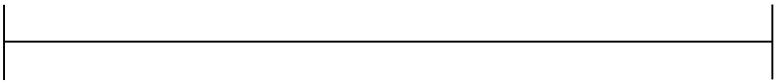
1. How likely would you be to use this product again if it was offered to you by a close friend?

NOT AT ALL LIKELY EXTREMELY LIKELY



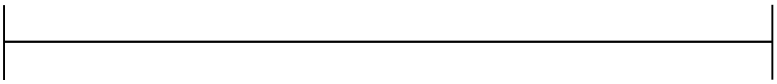
2. How likely would you be to buy this product for personal use?

NOT AT ALL LIKELY EXTREMELY LIKELY



3. How likely would you be to recommend this product to a smoker who is trying to reduce or quit smoking?

NOT AT ALL LIKELY EXTREMELY LIKELY



4. Do you think there was nicotine in the product you used today?
    a. Yes
    b. No