2018

THE SELF-REPORTED AND BEHAVIORAL EFFECTS OF PROPYLENE GLYCOL AND VEGETABLE GLYCERIN IN ELECTRONIC CIGARETTE LIQUIDS

Arit M. Harvanko
University of Kentucky, arit.h@uky.edu
Digital Object Identifier: https://doi.org/10.13023/etd.2018.273

STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's thesis including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Arit M. Harvanko, Student

Dr. Thomas H. Kelly, Major Professor

Dr. Mark T. Fillmore, Director of Graduate Studies

THE SELF-REPORTED AND BEHAVIORAL EFFECTS OF PROPYLENE GLYCOL AND VEGETABLE GLYCERIN IN ELECTRONIC CIGARETTE LIQUIDS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences at the University of Kentucky

By

Arit M. Harvanko

Lexington, Kentucky

Director: Dr. Thomas H. Kelly, Professor of Psychology

Lexington, KY

2018

ABSTRACT OF DISSERTATION

THE SELF-REPORTED AND BEHAVIORAL EFFECTS OF PROPYLENE GLYCOL AND VEGETABLE GLYCERIN IN ELECTRONIC CIGARETTE LIQUIDS

Little is known about how electronic cigarette (EC) users manipulate device parameters, what factors drive their use, and how non-nicotine ingredients influence the stimulus effects of EC aerosols. The ingredients propylene glycol (PG) or vegetable glycerin (VG) serve as the base for virtually all electronic cigarette liquids, and information on how they affect the using experience would provide important groundwork for the study of other ingredients. In this dissertation, results from a survey and laboratory study focused on the stimulus effects of ECs, and the influence of PG and VG, will be discussed. A total of 522 regular EC users completed a survey comprised of an electronic cigarette dependence questionnaire, questions on tobacco and electronic cigarette use, and device and liquid preferences. This was followed by a laboratory study with sixteen electronic cigarette users completing five test days (one practice and four assessment days). In the laboratory study, following one hour of nicotine deprivation, two sampling puffs from liquid formulations containing 100/0, 75/25, 50/50, 25/75, and 0/100% PG/VG concentrations were administered in random order during five assessments, each separated by 20 min. Primary outcome measures were self-reported stimulus characteristics and breakpoint on a multiple-choice procedure. Survey results indicated that ability to change device voltage, and level of resistance, was significantly associated with level of nicotine dependence, as was amount of liquid consumed, nicotine concentration, and milligrams of nicotine used per week. Participants also rated 'good taste' as the most important consideration when purchasing and using liquids, and PG was associated with undesirable effects and VG with desirable effects. Laboratory results indicated that greater VG content was associated with greater reports of visibility of the exhalant (i.e. “cloud”). Liquids with mixtures of PG or VG were associated with conventional cigarette smoking sensations and greater reductions of systolic blood pressure compared to formulations with only PG or VG. There was no significant effect of liquid formulation on the multiple-choice procedure, but puffs were rarely chosen over even the smallest monetary option ($0.05), suggesting minimal reinforcing efficacy. In conclusion, survey data indicate that a wide range device parameter settings and liquid ingredients are preferred by daily e-cigarette users, and that individuals with greater

nicotine dependence favor voltage control devices, and lower resistance heating elements. Survey data also indicated that taste is a key factor for EC liquid selection, and relative concentrations of propylene glycol and vegetable glycerin may have a significant impact on the reinforcing effects of liquids. In contrast, laboratory data suggests that PG or VG do not significantly impact the abuse liability of EC liquids, though reinforcing effects of these ingredients was unclear in the laboratory study.

KEYWORDS: Abuse liability, smoking, nicotine, withdrawal, electronic cigarettes

Arit Harvanko

July 9, 2018

THE SELF-REPORTED AND BEHAVIORAL EFFECTS OF PROPYLENE GLYCOL AND VEGETABLE GLYCERIN IN ELECTRONIC CIGARETTE LIQUIDS

By

Arit M. Harvanko

Dr. Thomas H. Kelly
Director of Dissertation

Dr. Mark T. Fillmore
Director of Graduate Studies

July 9, 2018

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE: ABUSE LIABILITY OF ELECTRONIC CIGARETTES

1.1 Introduction to Abuse Liability and Electronic Cigarettes

In the following dissertation the abuse liability of electronic cigarettes (EC) will be discussed. First, it is necessary to define abuse liability. Previous definitions of abuse liability have divided it into two sub-parts: "liability for abuse" and "liability of abuse" (Griffiths et al., 1987). Liability *for* abuse refers to the likelihood that a drug will be used for non-medical reasons – either as any use of a drug, or use of a medically prescribed drug in excess. Liability *of* abuse refers to the undesirable aspects of drug use (e.g. physical or social consequences to the user).

Predicting abuse liability of a drug is critical for assessing likelihood of abuse or off-label usage of therapeutic drugs before or after they go to market, and to determine the mechanisms driving misuse of drugs to facilitate development of treatment or regulatory approaches to lessen the negative impacts of drug abuse. Drug abuse liability is commonly assessed by examining human behavior in a laboratory setting. When examining abuse liability in a laboratory setting it is important to ensure proper control of experimental conditions, such as: presence of non-study psychoactive drugs, participant nutrient levels, and other variables that may influence study outcomes (Griffiths et al., 2003). As with the study of therapeutic drugs, it is also important to control for participant and experimenter expectations by using double-blind placebo-controlled study design. With nicotine and other drugs, consideration of drug use history requires careful consideration; withdrawal, for example, may alter a drug's abuse liability. Individuals who are experiencing withdrawal from a drug will likely respond differently on abuse liability measures compared to when they are not experiencing withdrawal symptoms

(e.g. Bell et al., 1999). As such, it is necessary to measure withdrawal symptoms, which can be drug specific, in order to capture possible influence of withdrawal alleviation on abuse liability.

Several types of outcome measures are typically used to assess a drug's abuse liability in a laboratory setting. Measures can include subject ratings related to likelihood for the drug to be abused. Such ratings are often input by study participants using a visual analog scale and can include items associated with drug liking or desire to use the drug again. To assess liability *of* abuse, subject-ratings focused on potentially undesirable effects (e.g. nausea, anxiety, "bad-effects") are typically incorporated. To assess liability *for* abuse, ratings focused on potentially desirable effects (e.g. feeling "high" or experiencing a "good effect") are often used. More direct measures of drug taking behavior are also typically incorporated. These can include self-administration paradigms that require the participant to enter responses in order to receive additional drug (for review see Panlilio and Goldberg, 2007), or decision-making paradigms that require the participant to choose between the drug being studied and a reference alternate reinforcer with a well characterized value (e.g. money or a drug with well-characterized abuse liability) (e.g. Griffiths et al., 1993). Although it may often be the case that drug-taking is associated with self-reports of desirable effects, these measures are not always concordant (i.e. if a given drug dose is particularly high, participants may report experiencing desirable effects while emitting fewer responses to receive more drug relative to a lower dose). Therefore, comprehensive assessments of liability for abuse include direct measures of drug-taking behavior in addition to self-reported drug effects. In addition to the aforementioned measures, physiological measures such as heart rate

and blood pressure, and some indication of biological drug concentration (e.g. breath or plasma drug concentration), are typically collected to account for individual and between-session differences in drug effects.

Popularization of ECs is relatively recent, (the first largely successful EC was developed in China around 2005 [Lik, 2005]), and the first laboratory studies of EC abuse liability were published in 2010. Although a new product, a long history of conventional cigarette (CC) research greatly informed early EC abuse liability work because of their shared inclusion of nicotine. For example, CC's engender well-characterized acute effects (Perkins et al., 1994), and tobacco deprivation among regular smokers consistently produces a common set of withdrawal symptoms (e.g. Hughes and Hatsukami, 1986). Leveraging this history of CC research, in one of the first EC abuse liability studies Vansickel and colleagues (2010) assessed two early generation, low power, ECs in a population of CC smokers following 12 h of CC deprivation. Abuse liability was measured by examining plasma nicotine concentration (nicotine being a drug with well documented abuse liability), and subject reports of drug liking and alleviation of CC withdrawal symptoms. Interestingly, the results of this study did not indicate significant elevation of plasma nicotine concentration following use of these early generation ECs. Yet, participants did indicate alleviation of some CC withdrawal symptoms – though to a lesser extent than a CC – suggesting that ECs would have some abuse liability among individuals experiencing CC withdrawal symptoms, perhaps by providing stimuli other than nicotine acting in the central nervous system (e.g. sensations associated with inhalation of nicotine or other stimulus effects associated with CC use). In a later study by Vansickel and colleagues (2012), abuse liability of ECs was assessed

among a sample of CC smokers – following 12 h of CC deprivation – using a decision-making paradigm (the Multiple Choice Procedure), which offered participants the ability to choose between puffs from an EC or an amount of money. Contrary to their earlier study, the EC now significantly increased plasma nicotine concentration. Using a CC as a comparator, choices for 10 puffs from the EC in this study had a lower breakpoint (point at which money was chosen over puffs) than choices for three puffs from a CC ($1.06 versus $1.50, respectively). These data suggest that ECs have some abuse liability among CC users following CC deprivation, but perhaps less than CCs.

In a review of the scant literature on the abuse liability of ECs in 2013 that included the two previous studies, Evans and Hoffman (2014) noted that data on the abuse liability of ECs was inconsistent. It was noted that a possible reason for this inconsistency is differences in history of EC use by participants in laboratory studies. Evans and Hoffman (2014) note that in studies measuring puff topography of ECs participants would inhale longer (i.e., longer puff duration), and ECs required more effort to draw air through compared to CCs. Thus, it may be that individuals with no EC experience (e.g. only CC experience) must learn to account for differences in the inhalation aspects of CCs and ECs. This possibility is supported by the lack of significant plasma nicotine increases among EC naïve participants in Vansickel et al. (2010), while experienced EC users have significantly increased plasma nicotine concentrations in other studies (e.g., Dawkins and Corcoran, 2014). Another issue likely affecting consistency of study results is the wide variety of EC devices and their settings, as well as the large variety of liquids for ECs.

Taken together, the extant literature suggests that ECs can have abuse liability, as assessed by abuse liability measures successfully used to study other drugs of abuse. Because the abuse liability of CCs is well characterized in the natural ecology as a reinforcer that is often used despite many possible negative consequences, this comparator has provided a useful benchmark to compare ECs to in the laboratory. Research has not yet, however, examined the abuse liability of ECs among individuals with no CC history, making it difficult to know the independent abuse liability of ECs. Additionally, due to differences potentially caused by history of EC use (or lack therein), the inconsistency of laboratory results on EC abuse liability suggests that other factors need to be considered. The following sections will outline some of these factors and how recent research has examined their influence on EC abuse liability.

1.2 Effects of Liquid Nicotine Concentration

Though perhaps not the only ingredient contributing to the reinforcing effects of CCs or tobacco more broadly, it has been well-known for decades that nicotine is a powerful reinforcer. Documents from the tobacco industry dating back to as early as 1963 indicate there has long been some awareness that "nicotine is addictive" (ASH, 1998). Converging evidence from laboratory studies over the past few decades have demonstrated that nicotine is a powerful reinforcer for animals and humans via multiple routes of administration (Stolerman and Jarvis, 1995). With regards to nicotine in ECs, despite common availability of non-nicotine containing EC liquids (e.g., most specialty EC stores stock liquids for sampling which must not contain nicotine), recent data suggests that EC users are purchasing liquids that contain nicotine 99.0% of the time (Marynak et al., 2017), making it likely that nicotine is a primary factor in the liability for abuse of ECs.

As previously mentioned, research on the effects of nicotine in EC liquids has been mixed on whether they can deliver clinically significant amounts of nicotine. Vansickel and colleagues (2010) examined two different types of early ECs containing 16 or 18 mg/ml nicotine concentrations and found that 10 puff bouts did not significantly elevate plasma nicotine levels among EC naïve participants. The use of these ECs did, however, reduce some subjective reports of tobacco abstinence, but to a lesser extent than a CC. In a similar study, Bullen and colleagues (2010) found little increase of plasma nicotine among EC naïve individuals following 60-min ad-lib use of an EC with 16 mg/ml nicotine concentration. In a later study by Vansickel and colleagues (2012), however, significant increases of plasma nicotine concentration were observed. In this study ECs were administered to individuals with experience using ECs, with aerosol being dispensed from devices and liquids the participants provided, and nicotine concentrations ranging between 9-24 mg/ml. Following a 1 h ad-lib puffing period, plasma nicotine concentrations reached levels comparable to those achieved following CC use (i.e. *mean*=16.3 ng/ml). As Evans and Hoffman (2014) point out, lack of experience with ECs may explain why the previous two studies did not find significant increases in plasma nicotine. In Vansickel et al (2012), although several factors were changed relative to previous studies (e.g. device parameters, EC use experience, liquid nicotine concentration), it was proven that ECs are capable of providing significant levels of nicotine. Later work has gone on to show that ECs are capable of increasing plasma nicotine to levels exceeding those typically observed following CC administration (Ramoa et al., 2015).

Laboratory research has shown a positive correlation between nicotine concentration in EC liquids and the nicotine yield of EC aerosols (Talih et al., 2014),

suggesting there would be a dose dependent increase in plasma nicotine concentration as nicotine concentration in liquids is increased. This has been demonstrated in laboratory studies examining multiple liquid nicotine concentrations, with pharmacokinetic delivery profiles closely resembling that of CCs (Ramoa et al., 2015; Lopez et al., 2016). Laboratory research on the behavioral effects of multiple nicotine concentrations in ECs has, however, been less clear. Harvanko and colleagues (2017) examined behavioral effects of three liquid nicotine concentrations (0, 8, and 16 mg/ml) among non-regular EC users in a laboratory study with controlled puffing conditions (i.e. 10 five second puffs) and found no significant indication of dose-dependent nicotine effects. Similar to the aforementioned studies, this may be because individuals in this study did not have adequate experience using ECs, which may have limited the ability of the ECs to cause significant behavioral effects. Dawkins and colleagues (2016) examined effects of two liquid nicotine concentrations (6 and 24 mg/ml) among experienced EC users who were allowed to puff ad libitum for 60 minutes. Results indicated that participants engaged in some compensatory puffing, such that more puffs – with greater duration – were taken in the 6 mg/ml compared to 24 mg/ml condition. Despite some compensatory puffing, significantly greater plasma nicotine concentrations were observed in the 24 mg/ml condition, but interestingly there were no significant differences between conditions on alleviation of self-reported nicotine withdrawal symptoms or other subjective effects.

Although research on the topic of how nicotine in EC liquids affects abuse liability is still scant, results of these few studies demonstrate that ECs are capable of delivering nicotine comparable to CCs, and that greater liquid nicotine concentrations engender greater plasma nicotine concentrations in the conditions of the previous studies. This

suggests that ECs could have a high liability for abuse based on their delivery of nicotine alone, though it is unclear whether it would rival that of CCs. Interestingly, none of the studies examining multiple nicotine concentrations noted significant differences in behavioral effects as a function of nicotine concentration. It could be speculated that this is because users compensate for differences in liquid nicotine concentration by modulating their puffing behavior. But, even when significant differences in plasma nicotine concentrations as a function of liquid nicotine concentration were observed (e.g. Dawkins et al., 2016), behavioral effects did not differ correspondingly. As such, these data might suggest that liquid nicotine concentration itself is not the sole determinant of abuse liability. With this limited amount of data, however, it is difficult to make definitive statements about the role of nicotine in EC liquids. As such, future research should continue to examine the effects of liquid nicotine concentrations on EC abuse liability in carefully controlled studies.

1.3 The Influence of Device Parameters

Electronic cigarettes can have a myriad of parameters that are adjustable by the user and research has begun to delineate the ways in which these parameters affect nicotine delivery and the EC using experience. Shihadeh and Eissenberg (2015) outline parameters (e.g. heating element configuration, power levels, liquid tank design) that likely play a role in the "dose and rate" at which ECs can deliver nicotine to the user, which suggests these parameters could also play a role in ECs' liability for abuse. For example, parameters associated with the power provided to the heating element (typically identified by the arithmetically related variables: $wattage = \frac{voltage^2}{resistance}$) likely alter nicotine delivery to the user. Research by Gillman and colleagues (2016) has

demonstrated that when using machine puffing conditions, there is a systematic increase in aerosol yield when power (wattage) is increased, which has also been replicated in another study (Talih et al., 2014). This indicates that power is likely a significant factor in the ability of ECs to deliver nicotine to the user. Unfortunately, no laboratory studies have directly tested this possibility.

There has been much concern about the composition of EC aerosols as a function of power levels. Kosmider and colleagues (2014) tested the effect of differing power levels on presence of carcinogenic aldehydes (e.g. formaldehyde or acetaldehyde) in EC aerosols and found a significant positive correlation between power and aldehyde production. Subsequent studies replicated this effect (Geiss et al., 2016; Jensen et al., 2015), leading to the question of whether ECs should be considered a harm-reduction tool for CC smoking. In response to this growing concern, Farsalinos and colleagues (2015) allowed experienced EC users to administer puffs from an EC at varying power levels and examined subjective effects, while simultaneously measuring aldehyde production in the same ECs at corresponding power levels. Results of this study showed that EC users would report a "dry-puff" condition (determined by reports of "bad-taste") at power levels causing high levels of aldehyde production. Based on these findings, Farsalinos and colleagues (2015) argue that EC users naturally avoid the aversive "dry-puff" condition and, as such, "exposure to formaldehyde from ECs is minimal to non-existent."

Another important EC parameter is the configuration of the heating element. Research has demonstrated that, while power levels play a role in nicotine and aldehyde production, the configuration of the heating element also affects aerosol composition. For example, Gillman and colleagues (2016) tested several different heating elements set

to the same power levels and found a wide range of aldehyde concentrations and overall particulate yields in EC aerosols. Another example is use of 'direct-dripping,' a method whereby liquid is placed directly on wicking material by the user, rather than relying on wicking action from a liquid tank on the EC. Talih and colleagues (2016a) found that aldehyde emissions from 'direct-dripping' greatly exceeded those from other ECs and even CCs, suggesting greater health risk using this method compared to tank type ECs. Mechanistically, heating element configuration can affect aerosol production by altering temperatures where liquid meets the heating element. Talih and colleagues (2017) explain that heating elements can utilize single or multiple coils, with greater number of coils distributing power over a larger total surface area, potentially reducing temperatures at the point of aerosolization. Unfortunately, research has not yet addressed the effects of heating element design on ECs when administered by humans. It could be speculated, however, that since amount of aldehyde emissions have been associated with aversive subjective effects (e.g. 'dry-puff,' Farsalinos et al., 2015), and heating coil configuration has been associated with aldehyde emissions, there could be a relationship between heating coil configuration and subjective effects. Future research is, however, necessary to test this hypothesis.

1.4 The Influence of non-nicotine ingredients

The predominance of research on EC liquid ingredients has focused on nicotine. Yet, EC liquids typically contain at least several ingredients, including a substance acting as a solvent or 'carrier,' which functions to suspending nicotine and make it viable for aerosolization. Two ingredient typically that act as a carrier substance and comprise the majority (e.g. 88-96% by weight, NJOY, 2013) of virtually all EC liquids, either alone or

in combination, are propylene glycol (PG) and vegetable glycerin (VG). In addition to PG and VG, inclusion of some amount of water, ethanol, and ingredients for the purpose of flavoring are commonly found in EC liquids (Etter and Bugey, 2017). In the United States, there are no EC specific ingredient requirements, and no requirement to label liquid contents. Though some manufacturers will voluntarily display listings of some ingredients (e.g. PG and VG ratio [but not total volume], and nicotine concentration), comprehensive ingredient labels are virtually non-existent. Food and Drug Administration regulation currently being phased in, however, will require all manufacturers to disclose EC ingredients. Though, it is unclear if and when this information will be publicly available. This lack of standardized labelling, amid an enormous variety of different liquids being manufactured (e.g. an estimated 7,764 in 2014 [Zhu et al., 2014]), has made examination of non-nicotine liquid ingredients challenging for two reasons: 1) in order to know what ingredients are in EC liquids chemical analyses must first be conducted, and 2) even when ingredients are identified for experimental examination it is not known how common the ingredients are in other liquids (i.e. how generalizable the results will be).

Despite challenges with identifying specific chemicals added to EC liquids for flavoring, a few laboratory studies have examined the role of flavor as a whole in ECs. For example, Audrain-Mcgovern and colleagues (2016) compared non-flavored and flavored EC liquids and showed that flavored liquids had significantly greater reinforcing effects. St. Helen and colleagues (2017) examined the effects of three different types of flavors among experienced EC users and found differences in subjective liking and plasma nicotine concentrations between flavors. Results of these studies demonstrate that

the addition of ingredients for flavoring can significantly increase EC liability for abuse by altering reinforcing effects, which may be associated with nicotine delivery. In the future manufacturers will hopefully be required to list ingredients in EC liquids, allowing researchers to examine the effects of specific flavoring additives so that a more robust and generalizable body of knowledge can be formed on this topic.

Since PG and VG are requisite components of EC liquids that comprise the bulk of liquid volume, and manufacturers often voluntarily include the relative ratio of PG and VG in liquids, these ingredients are a good candidate for research on non-nicotine ingredients in EC liquids. Laboratory analysis of aerosol production based on PG/VG ratio indicates that liquids with greater VG content produce greater light scattering coefficients (i.e. visibility of the aerosol) and that PG and VG play a role in nicotine yield of aerosols (Baassiri et al., 2017). Only one study, however, has examined the effects of PG and VG on plasma nicotine concentrations in humans and found that formulations containing some amount of PG led to greater plasma nicotine concentrations than formulations with VG alone (Yan and D'Ruiz, 2015). This study, however, did not examine multiple formulations across the spectrum of PG/VG ratios (e.g. 100/0% to 0/100% PG/VG), so it cannot be determined what the effects of PG alone are, or whether there is a clear dose-response relationship between PG/VG ratios and plasma nicotine concentrations. In addition to laboratory research, a survey of EC users suggests that PG is more closely associated with 'throat hit' (a term used to describe the sensation of EC aerosols on the throat) than VG (Etter, 2016a). There has not, however, been any research to investigate this possibility in a laboratory setting.

Since PG and VG are always present in EC liquids, and since the existing literature has not yet explored differences in subjective or reinforcing effects of PG and VG in EC liquids, this dissertation focused on examining these topics using a survey (Chapter 2) and laboratory study (Chapter 3) to determine if these ingredients may affect the abuse liability of ECs. As delineated in the prior sections ('the influence of nicotine' and 'the influence of device parameters'), there are several variables that can affect the EC using experience, which should be accounted for when studying these devices. As such, prior to conducting the laboratory study, the survey study was used to collect information on EC variables typically utilized. Based on results of this survey study, settings most commonly utilized (e.g. wattage and nicotine concentration) were selected for EC administration in the following laboratory study. The survey study was also used to assess associations EC users made with PG and VG and several subjective EC effects. These results then served as the basis for hypotheses about the subjective and reinforcing (i.e., stimulus effects) effects of PG and VG in the following laboratory study.

CHAPTER TWO: ELECTRONIC CIGARETTE LIQUID AND DEVICE PARAMETERS AND AEROSOL CHARACTERISTICS: A SURVEY OF REGULAR USERS

2.1 Introduction

Electronic nicotine delivery systems, and specifically 'electronic cigarettes' (ECs), represent a varied group of devices with user adjustable parameters, including heating element variables (such as heater coil configurations and power settings), and concentrations of nicotine, a variety of flavorants, and other ingredients in liquids. Early ECs (i.e. 'first-generation' ECs) were relatively simple devices that restricted the user from altering power levels and heater coil configurations, and typically limited liquids to only those sold for a specific device. ECs evolved from these simpler first-generation devices to more complex 2nd and 3rd generation devices. Key changes include heating element control by specifying wattage, voltage, or temperature, adjustable heater coil configurations (e.g. number, diameter, length, and materials of coils), and refillable tanks that allow the user to control liquid composition. Because ECs have many variables, it is necessary to understand how regular EC users utilize their devices and their parameters to construct relevant regulatory policy or maximize efficacy of ECs for smoking cessation.

One key function of ECs is to deliver nicotine, which is influenced by user-adjustable parameters. Previous laboratory research has demonstrated that concentration of nicotine in EC liquids can have a significant impact on the EC-using experience and the composition of the aerosols they produce. Expectedly, increases in liquid nicotine concentration have been shown to increase concentration of nicotine in EC aerosols (Talih et al., 2014) and plasma nicotine levels following EC use, with plasma nicotine

levels following high nicotine concentrations (i.e. 3.6% nicotine) exceeding levels typically achieved from conventional tobacco cigarettes (CCs) (Ramoa et al., 2016). The nicotine concentration in EC liquids has also been demonstrated to have a negative relationship with puff topography, such that EC users will take shorter duration puffs from ECs containing higher nicotine concentrations compared to lower concentrations (Lopez et al., 2016). Lastly, previous research has shown that liquids with greater proportions of propylene glycol (PG), relative to vegetable glycerin (VG), increases nicotine concentration in EC aerosols, which may suggest that PG/VG concentrations could alter plasma nicotine concentrations following EC use (Talih et al., 2016b).

It has also been suggested that EC device parameters affect the level of nicotine emitted by ECs. Shihadeh and Eissenberg (2015) provide a framework for understanding the level of nicotine emitted by ECs, emphasizing that many different EC variables impact nicotine emission. Variables in this framework include: liquid container design (e.g. cartomizer, tank, drip tip, disposable), heating element parameters (electrical resistance, voltage, and surface area of the heating coil), liquid variables (nicotine concentration, solvent composition, flavoring, and other additives), and usage behaviors (puff duration, inter-puff interval, and number of puffs). Since these variables likely affect nicotine delivery, they also likely affect the abuse liability of ECs. Additionally, these variables can influence the potential harm of ECs. For example, voltage level (directly associated with wattage when coil resistance is held constant), is associated with emissions of carcinogens from ECs (Kosmider et al., 2014). Other research has demonstrated that constituents in EC liquids – namely PG and VG – can degrade into

carcinogens when used in an EC. Yet, whether regular EC users typically use ECs in a manner that would lead to high levels of carcinogen emission is not well studied.

It is important to know what factors motivate the initiation and continued use of ECs in order to more completely understand their abuse liability and efficacy as potential smoking cessation tools. Farsalinos and colleagues (2013) reported that the majority of EC users in their sample use multiple different flavors within a day, and that ECs would be 'less enjoyable' if flavor availability were limited. Therefore, taste might drive both the initiation and continuation of EC use. It is unclear from these data, however, what the relative contribution of taste is compared to other possible motivations for initiation and continuation of EC use. Users of ECs have also identified "throat hit" as an important stimulus characteristic, with reports suggesting that liquid and device parameters (e.g. use of higher liquid nicotine concentrations) may be associated with this effect (Etter, 2016a), though whether device power (i.e. wattage) is associated with throat hit is not yet known.

In August 2016, a Food and Drug Administration (FDA) rule came into effect that placed ECs under FDA regulation. Now that there is a regulatory mechanism for ECs it is important to study behaviors of regular EC users. Behaviors of regular EC users may, for example, highlight usage patterns that put individuals at undue health risk, which would provide an important regulatory target. Knowing common EC settings and usage patterns will also inform future research, such that studies can utilize the most common EC user settings to determine if these settings confer significant health risks to the user. The extant literature is lacking estimates from a broad sample of regular EC users on key variables that likely influence the reinforcing effects of ECs, their potential harms, and motivations for initiation and continued use of ECs. This poses several problems: 1) it is

difficult to conduct generalizable research on ECs without knowing what adjustable parameter settings are commonly used, 2) it is difficult to assess health risks associated with ECs without knowing whether settings that could cause harmful effects are commonly used, and 3) it is difficult to employ meaningful regulation without first understanding how ECs are being used. To address this gap in the extant literature, a survey of regular nicotine-dispensing EC users in the United States was conducted. The primary goal of the survey was to determine how adjustable parameters are typically used, the factors that motivate EC liquid selection, and the factors that influence initiation and continuation of EC use. Also examined was the association between nicotine dependence and (1) frequency of EC use, (2) adjustable settings, and (3) liquid preferences. Results of this survey will support the translation of laboratory research findings to the natural ecology, and to inform EC-related public health policy efforts.

2.2 Methods

2.2.1 Participants

A non-EC internet marketplace (Amazon's Mechanical Turk [mTurk]) was used to recruit study participants. A listing on the site invited EC users to complete the survey during the spring of 2016. Participants were first asked 10 screening questions to verify EC use and establish eligibility. To complete the full survey, participants were required to: report daily use of an EC – with liquids containing nicotine – throughout the past month, use ECs as their primary means of administering nicotine, have a 95% or higher approval rating on previously completed mTurk tasks, and be over 18 years of age.

2.2.2 Overall Procedure

Participants were required to complete all questions applicable to them, and were not shown questions that did not apply to them (e.g. if a participant indicated not currently using tobacco, they were not presented questions regarding tobacco use). To minimize duplicate entries, the survey could be completed on a specific computer only once. This study was approved by the University of Kentucky Institutional Review Board.

2.2.3 Measures

The survey was comprised of several sub-sections: a nicotine dependence questionnaire (the Penn State [Electronic] Cigarette Dependence Index), tobacco and electronic cigarette usage history, device preferences, and liquid preferences.

Penn State [Electronic] Cigarette Dependence Index (PSCDI). This scale contains 10 questions regarding use of electronic and tobacco cigarettes and behaviors associated with nicotine dependence (Foulds et al., 2015). Scores range from 0-19, with higher scores indicating greater dependence on electronic and tobacco cigarettes.

Tobacco and Electronic Cigarette Usage History: This experimenter-designed section consisted of seven items assessing quantity and frequency of EC usage, and reasons for initial and continued use. Questions included: 'do you own an electronic cigarette [yes/no],' 'were you a regular tobacco user prior to using an electronic cigarette,' 'are you currently trying to quit using tobacco products,' 'are you currently trying to quit using tobacco products by using electronic cigarettes,' 'how long ago did you begin using an electronic cigarette regularly,' 'why did you first begin using an electronic cigarette,' and 'why do you continue to use an electronic cigarette?' For the last two questions,

participants were given a list of possible options to choose from, including an option to write-in an unlisted reason.

Device Preferences: This experimenter-designed section was comprised of six items assessing the type of EC participants typically use and its parameter settings. Questions included: 'what is the brand of your preferred electronic cigarette tank,' 'can you change the voltage of the electronic cigarette that you typically use,' 'what voltage do you typically use,' 'what is the typical resistance (in ohms) of the coils,' 'how many watts do you typically use,' 'is the electronic cigarette you typically use rechargeable?' In order to facilitate accurate responses an annotated picture of a common EC coil was shown to the participant describing how to determine coil resistance.

Liquid Preferences: This experimenter-designed section was comprised of eight items assessing EC liquid preference. Participants were asked: what types of liquid they purchase ('pre-filled disposable tanks or cartridges,' 'pre-mixed ready-to-use liquids for refillable tanks,' 'mix own liquids using basic ingredients'), how much liquid they use per week (in ml or number of cartridges). Participants were also asked if they 'pay attention to the amount of nicotine' in the liquids they use and, if so, what the 'nicotine concentration of the liquids' they 'typically use in mg/ml.' Participants were asked to rate 'what effects of electronic cigarette liquid are most important to you,' and 'when purchasing or making electronic cigarette liquids what factors are most important to you,' with possible answers based on previous research indicating common factors EC users consider when selecting liquids (Farsalinos et al., 2014a). Ratings of these factors were entered using a 100-point scale anchored with 'least important' and 'most important' on either end. Participants were also asked if they 'pay attention to the amount of propylene glycol (PG) and vegetable

glycerin (VG) in EC liquids' and, if so, the percentage of PG and VG in the liquids they typically use, and whether liquids with more PG or VG are most closely associated with several effects. Ratings were entered on a 100-point scale anchored on one end with 'PG,' and 'VG' on the other.

2.2.4 Data Analysis

Descriptive statistics were used to examine distributions of demographic variables, device parameter preferences, and liquid preferences. Milligrams of nicotine used per week was estimated based on milliliters of liquid used per week and nicotine concentration typically used. To examine possible relationships of nicotine dependence with tobacco usage behaviors, liquid and device preferences, and subjective effects, correlational analyses were conducted between total score on the PSCDI and items from the tobacco and EC usage history, device preferences, and liquid preferences questionnaires. Since the PSCDI includes an item directly related to quantity of EC use (i.e. "How many cigarettes and times per day do you usually smoke or use your electronic cigarette?"), total scores were recalculated omitting this item for correlational analysis involving other direct measures of EC use (i.e. number of milliliters, disposable cartridges, or milligrams of nicotine used per week). Based on previous data indicating that nicotine concentration is associated with "throat hit," (Etter, 2016a) ratings of "throat hit" and parameters (power, power multiplied by nicotine concentration, and milligrams of nicotine used per week) impacting nicotine exposure were also examined. To examine whether subjective EC effects were more closely associated with PG or VG, differences from the midpoint were evaluated using *t*-tests. The alpha value for all analyses was set at $\leq .05$.

2.3 Results

A total of 1,586 participants answered screening questions, and the 522 individuals that met inclusion criteria completed the entire survey. Participants were comprised of 290 (55.7%) females with an average age of 33.0 (*SD*=10.2). Descriptive statistics are shown in tabular form for usage behaviors and settings (Table 2.1) and liquid variable preferences (Table 2.2).

Fifty-nine percent of individuals endorsed currently using at least one other tobacco product in addition to ECs. Endorsement of current use of another tobacco product (i.e. cigarettes, snus or chewing tobacco, cigars, or hookah) was associated with significantly higher scores on the PSCDI (i.e. level of nicotine dependence, Table 2.1). Not having used other tobacco products besides ECs was negatively associated with PSCDI scores (Table 2.1), with never other tobacco product users having lower PSCDI scores (*m*=6.1, *SD*=4.4) compared to past other tobacco product users (*m*=9.81, *SD*=4.0) and current other tobacco product users (*m*=10.3, *SD*=3.58), and no significant differences in length of EC use were found between these groups. Two parameter setting preferences were significantly associated with PSCDI scores, heater coil resistance (in ohms) and ability to change voltage on the device (Table 2.1). Among the 197 individuals who knew the wattage they typically used and who provided ml's of liquid typically used per week, there was a positive correlation between wattage and ml's used (*r*=.20, *p*=.005).

When asked to rate "what effects of liquids are most important to you" from 'most Important' (100) to 'least important' (0), participants rated 'good taste' (*m*=87.3, *SD*=15.7), 'does not cause sore throat' (*m*=77.3, *SD*=23.4), and 'does not cause headache' (*m*=76.7, *SD*=26.3) as the three most important factors (Figure 2.1). When asked 'when purchasing

or making liquids what factors are most important to you' participants again indicated that the most important factor is 'good taste' (m=88.0, SD=13.6), followed by 'availability' of the liquids (m=73.8, SD=23.0), and 'decreased health risks, avoid certain ingredients' (m=73.4, SD=27.0), and 'low price' (m=72.6, SD=24.3). 'Throat hit' received a more moderate rating of importance (m=65.8, SD=28.0). A significant correlation was found between ratings of the importance of 'throat hit' and nicotine concentration (r=.19, p<.001) and milligrams of nicotine consumed per week (r=.14, p<.019), but not power or nicotine concentration multiplied by power.

The majority of users (74.2%) indicated using liquids purchased for ECs with refillable containers (further separable as 'pre-mixed' liquids [64.8%] or liquids mixed by the end-user from basic ingredients [9.4%]), and while no differences in nicotine dependence scores were observed as a function of type of liquid purchased, amount of liquid used was positively correlated with PSCDI scores (Table 2.2). Seventy percent of individuals reported paying attention to the nicotine concentration of the liquids they typically used, and nicotine concentration was positively correlated with PSCDI scores (Table 2.2). Among the 188 (36.0%) individuals who indicated wattage and nicotine concentration typically used, there was a significant negative correlation between these two variables (r(188)=-.23, p=.002). Among 285 (54.6%) participants who reported paying attention to nicotine concentration and milliliters of liquids used for refillable devices, milligrams of nicotine used per week was positively correlated with PSCDI scores (Table 2.2). Lastly, 239 (45.8%) individuals reported paying attention to the amounts of PG and VG in the liquids they typically use, and this was not significantly correlated with PSCDI scores.

When asked to rate which effects were more closely associated with PG or VG, participants indicated that PG was more closely associated with dry mouth ($t[237]=6.232$, $p<.001$), sore throat ($t[237]=7.432$, $p<.001$), headache ($t[237]=6.909$, $p<.001$), and dizziness ($t[237]=4.417$, $p<.001$). VG was significantly associated with large cloud ($t[237]=6.794$, $p<.001$), good smell ($t[237]=8.102$, $p<.001$), and good taste ($t[237]=6.607$, $p<.001$). Throat hit was not significantly associated with PG or VG.

2.4 Discussion

This study addresses critical gaps in our understanding of EC use by providing detailed information on EC usage behaviors, device parameter settings, and liquid variables among regular (i.e. daily) EC users. EC users utilize a wide variety of devices, power levels (i.e. watts, volts, ohms), and nicotine concentrations. These data suggest that no predominant combinations of user-adjustable products have emerged from the broad range of commercial options. Consistent with previous findings (Farsalinos et al., 2014a), taste was identified as the most important variable when using ECs or purchasing liquids. Desirable effects were associated with the ingredient VG, and undesirable effects with PG, suggesting that these ingredients might influence the reinforcing effects of ECs.

One of the primary goals of this survey was to determine the adjustable parameter settings typically used. Key among these settings is wattage, a measure of power output that is arithmetically related to voltage and resistance by the equation: $wattage = \frac{Voltage^2}{Resistance}$. The median wattage reported is approximately 10 watts, but many individuals reported setting their ECs to power levels of up to 10 times greater (100 watts), indicating that a wide range of power levels are utilized. Many individuals indicated not knowing the wattage of their device (57.7%), which is comparable to previous research where

most participants reported not knowing the voltage (51.5%) or resistance (63.6%) of their devices (Rudy et al., 2017). This indicates a need for more reliable, and potentially more objective, approaches to determining common EC parameter settings. It should be noted that the wattage scale was limited to 0-100 watts, as at the time of this survey few, if any, popular EC manufacturers offered devices capable of delivering more than 100 watts. For example, in late 2015 the most commonly used brand of device by participants in this survey (Kangertech, used by 15.5% of participants) offered power supplies rated to a maximum of 60 watts (Kangertech, 2017a). More recently, however, this brand began offering products capable of delivering up to 200 watts (Kangertech, 2017b). A recent study by Wagener and colleagues (2017) also measured wattage ratings of a small sample of third-generation ECs and found power levels exceeding 100 watts. Thus, 100 watts may have been too low of a threshold, and greater power levels may have been used at the time of this survey, or since the completion of this survey. Despite this potential limitation, data on power levels has a right skewed distribution with a mean of 28.3 watts and *SD* of 24.2 (Figure 2.3), suggesting that most users utilized power levels below 100 watts. Importantly, future research should closely monitor changes in power settings since previous research has indicated a positive relationship between power levels and amount of potentially harmful chemicals in EC aerosols (Jensen et al., 2015; Kosmider et al., 2014).

Overall scores on the PSCDI in the current study were slightly higher than scores among exclusive EC users in a previous study (*m*=8.1) (Foulds et al., 2015). Participants in Foulds and colleagues (2015) were exclusive EC users with a history of CC use. Comparing ex-CC smokers from the current study, average PSCDI scores were still

slightly higher (i.e. m=9.8, SD=4.0). It could be speculated that this is because use of newer ECs (i.e. those introduced following Foulds et al. [2015]) is associated with higher levels of nicotine dependence, particularly if ECs are used in a manner that causes plasma nicotine concentrations to exceed those typically seen following CC use (e.g. Ramoa et al., 2016). This is a concern shared by Cobb and colleagues (2015), who speculate that sole use of ECs may engender greater nicotine dependence than use of CCs. Yet, participants from the current study who reported no previous use of non-EC tobacco products reported significantly lower PSCDI scores compared to current or ex-CC smokers, suggesting that sole use of ECs with no CC history does not engender greater nicotine dependence.

Interestingly, wattage was not significantly associated with level of nicotine dependence (Table 2.1), but there were associations with ability to change voltage on the device and resistance of the heater coil. This may be related to type of device, as typically only 2nd or 3rd generation devices allow the user to adjust voltage and coil resistance, while 1st generation do not. The positive correlation between heater coil resistance and nicotine dependence may seem counterintuitive because lowering heater coil resistance while holding voltage constant would produce higher power levels. Additional research is required to further explore the relationships between use of a device with variable voltage and greater nicotine dependence, and between heater coil resistance and nicotine dependence.

The distribution of nicotine concentrations (Figure 2.3) indicates that the most common concentration is 3 milligrams/milliliter (.3%) with peaks at commonly sold nicotine concentrations (multiples of 3). Mean nicotine concentration was 9.1 (*SD*=7.2),

which is comparable to an estimate of 9.5 (*SD*=7.3) by Rudy and colleagues (2017). While there was not a significant correlation between wattage and nicotine dependence, there was a significant negative correlation between wattage and nicotine concentration, indicating that while individuals use a variety of power levels, nicotine concentration is decreased when power levels are increased. It should be noted, however, that more powerful devices may alter the rate of nicotine delivery (Farsalinos et al., 2014b). Amount of liquid used per week was positively associated with power levels. As such, it could be hypothesized that power level selections may impact weekly nicotine intake. There were significant correlations between nicotine dependence and (1) the amount of liquid typically used per week (as measured by disposable cartridges or milliliters of liquid), (2) typical nicotine concentration, and (3) quantity of nicotine used per week, with quantity of nicotine use per week serving as a better predictor of nicotine dependence than milliliters of liquid used per week (Table 2.2). These findings suggest that weekly intake of nicotine is a potentially useful measure for future EC research.

When asked "what effects of e-cig liquid are most important to you" or "when purchasing or making electronic cigarette liquids what factors are most important to you" respondents indicated that taste was most important. This is consistent with previous research indicating taste as the most important motive for EC use (Temple et al., 2017) and that regular EC users modify their devices primarily to improve taste (Etter, 2016b). Though "throat hit" was not ranked highly in importance among other stimulus characteristics in this study, consistent with Etter (2016a), it was positively correlated with nicotine concentration and, additionally, amount of nicotine consumed per week. This suggests that individuals who value throat hit may modulate nicotine concentration

and overall consumption to optimize this characteristic. When participants were asked which effects were most closely associated with PG and VG, PG was significantly related to potentially undesirable effects (dry mouth, sore throat, headache, and dizziness), while VG was associated with potentially desirable effects (large cloud, good smell, good taste). These results suggest that liquids with greater VG concentrations may have greater reinforcing effects, particularly since taste was indicated as the most important factor in liquid preference. It should be noted, however, that although participants indicated VG being more closely associated with desirable effects, on average participants used liquids containing approximately 1:2 ratios of PG and VG, suggesting that choice of PG/VG concentrations may not be driven exclusively by associated stimulus characteristics. One other possibility is that PG has been shown to increase nicotine yield in EC aerosols (Baassiri et al., 2017), which could play a role in the inclusion of PG in EC liquids.

Several potential limitations of this survey should be noted. First, participants in this study may not be representative of all regular EC users in the United States. For example, participants were required to use ECs containing nicotine to participate in this survey and therefore these results may not generalize to use of non-nicotine containing ECs. It could be speculated that individuals using ECs that do not contain nicotine may place greater importance on different subjective effects, and perhaps have lower nicotine dependence scores. These results may also not generalize to an adolescent population. Adolescents have had less opportunity to use other tobacco products and therefore may be more likely to initiate nicotine use with ECs. For example, a recent survey indicated that 9.9% of high school seniors used only an EC in the past month, while only 6.0%

reported using conventional cigarettes (McCabe et al., 2017), suggesting that exclusive EC use may be more frequent among high among adolescents than was observed in the current study. Second, not all EC users paid attention to certain device parameters (e.g. wattage, voltage, resistance) or liquid (e.g. nicotine concentration, PG/VG ratios) variables. As such, it is possible there were systematic differences between users who did and did not pay attention to these variables (e.g. individuals using early generation ECs may have been less likely to pay attention to device characteristics that are not modifiable or displayed on the device itself). Third, although careful steps were taken to increase reliability of reports on device and liquid characteristics (e.g. first confirming that users 'pay attention' to the variable in question before asking them to report the value, showing a picture of where heater coil resistance values are typically found on the device), it is still possible that users were inaccurate on reports of adjustable parameter settings. Lastly, although detailed information on EC parameters was collected, additional variables (e.g. heater coil configuration or heater coil materials) should be considered in future studies.

Table 2.1 Usage Behaviors and Settings

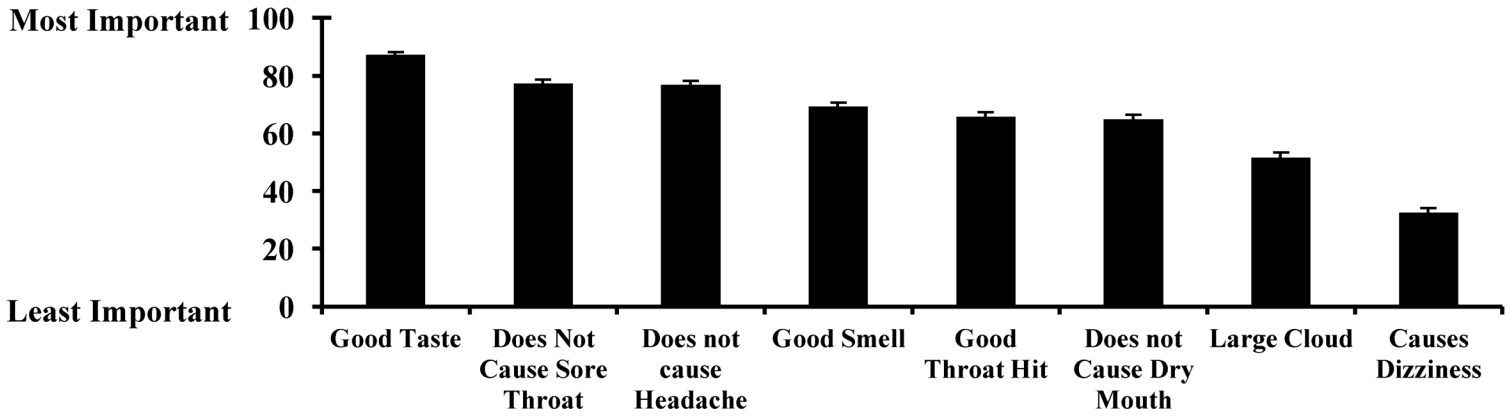
		Relationship with PSCDI, *r* (*p*)
Currently using ECs and other tobacco products, *N (%)*	308 (59.1)	.070 (.111)
Portion of other tobacco product users trying to quit, *N (%)*	261 (84.7)	.022 (.616)
Former regular user of other tobacco products, *N (%)*	180 (34.4)	**-.678 (<.001)**
Began regular other tobacco product use after ECs, *N (%)*	7 (1.3)	.003 (.952)
Never used tobacco products besides ECs, *N (%)*	34 (6.5)	**-.203 (<.001)**
Types of non-EC tobacco Used		
Tobacco cigarettes, *N (%)*	285 (54.6)	**.710 (<.001)**
Snus or chewing tobacco, *N (%)*	34 (6.5)	**.172 (<.001)**
Cigars, *N (%)*	52 (10.0)	**.190 (<.001)**
Hookah, *N (%)*	61 (11.7)	**.266 (<.001)**
Months of EC use, *mean (SD)*	13.9 (7.9)	-.007 (.876)
Penn State [Electronic] Cigarette Dependence Index Score, *mean (SD)*	10.0 (4.0)	--
Can you change the voltage on the EC you typically use, *N (%)*	315 (60.4)	**.257 (<.001)**
Typical power settings*		
Wattage (*N* = 221)**,** *mean (SD)*	28.3 (24.2)	.031 (.555)
Resistance in Ohms (*N* = 255)**,** *mean (SD)*	1.1 (0.8)	**.096 (.035)**
Voltage (*N* = 371)**,** *mean (SD)*	2.9 (1.8	.041 (.262)

EC= electronic cigarette. *Based on responses only from individuals indicating they knew what the wattage, voltage, or resistance they typically used was (*N* of these individuals indicated after each setting).

Table 2.2 Electronic Cigarette Liquid Variables		Association with PSCDI, Statistic (*p*)
Type of liquid/container typically used		
Disposable container, *N (%)*	131 (25.7)	*F* = .871 (.419)
Pre-mixed for refillable devices, *N (%)*	330 (64.8)	--
Liquid mixed by user from basic ingredients, *N (%)*	48 (9.4)	--
Amount of liquid typically used per week		
Number of disposable cartridges (25.7% of users)**,** *mean (SD)*	3.7 (2.9)	***r* = .288 (<.001)**
Milliliters of liquid for refillable devices (74.2% of users)**,** *mean (SD)*	22.9 (26.0)	***r* = .112 (.029)**
Typical nicotine concentration used (mg/ml) (*N*=366),* *mean (SD)*	9.1 (7.2)	***r* = .214 (<.001)**
Milligrams of nicotine used per week (*N*=285),† *mean (SD)*	192.5 (254.0)	***r* = .244 (<.001)**
Typical percentage of propylene glycol and vegetable glycerin (*N*=239)†		
Vegetable Glycerin**,** *mean (SD)*	63.3 (20.6)	*r* = -.060 (.388)
Propylene Glycol**,** *mean (SD)*	36.7 (20.6)	--

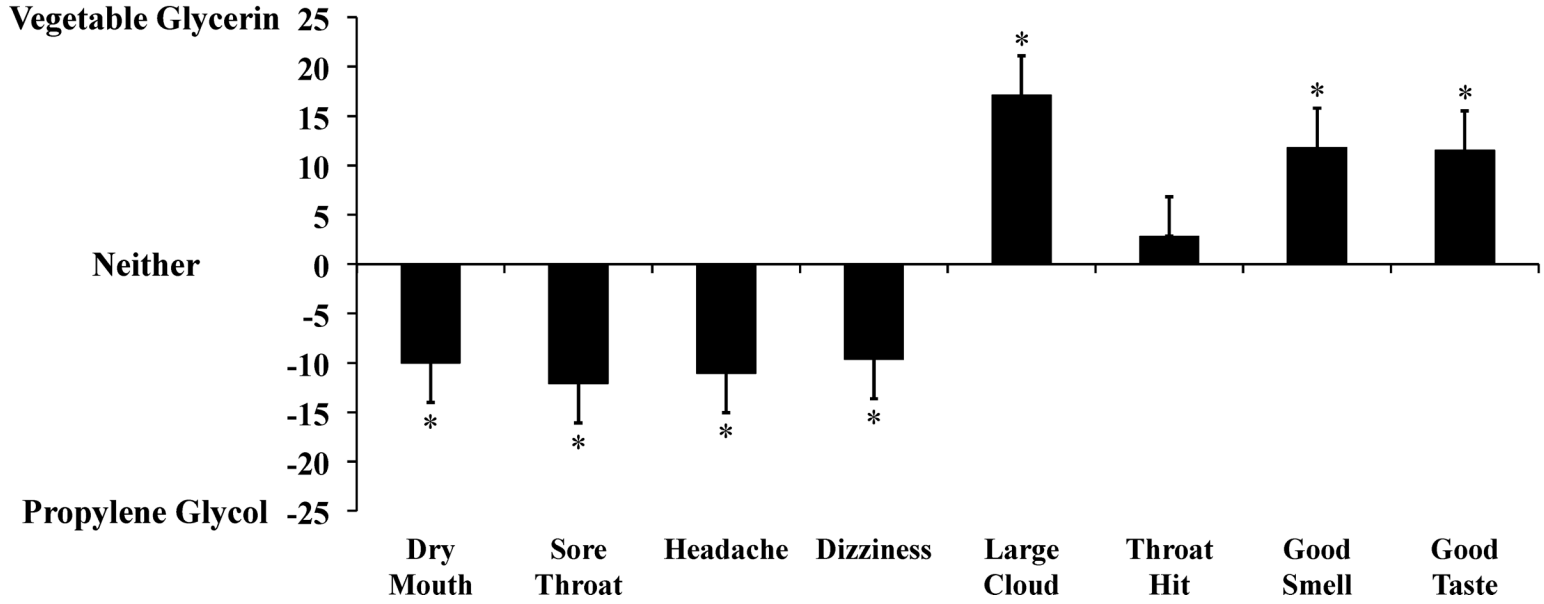
PSCDI= Penn State [Electronic] Cigarette Dependence Index. *Represents only individuals who reported paying attention to the nicotine concentration they typically used. †Calculated by multiplying reported mg/ml liquid nicotine concentration by milliliters of liquids typically used per week and represents only users who do not use disposable containers and who pay attention to the amount of nicotine in their liquids. †Amounts include only individuals who indicated that they "pay attention" to the amount of propylene glycol and vegetable glycerin in liquids.

Figure 2.1 "What effects of liquids are most important to you?"



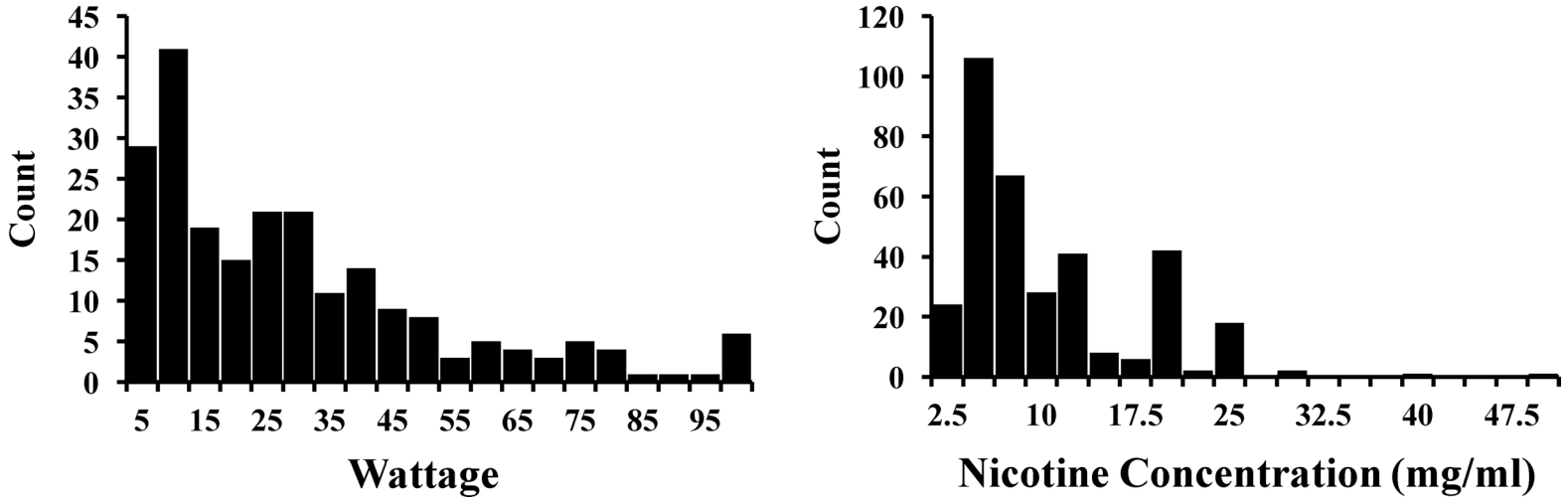
Participants were asked to rate all effects by placing a slider on a scale anchored on the left at 0 ("Least Important") and on the right at 100 ("Most Important"). Columns represent mean values and error bars represent standard error of the mean.

Figure 2.2 "Are vegetable glycerin or propylene glycol more closely associated with these effects?"



Participants were asked to rate whether these effects were more closely associated with propylene glycol or vegetable glycerin on a scale of -50 to +50, respectively, with 0 indicating neither. All effects except 'Throat Hit' were significantly different than 0 (*p*s<.05).

Figure 2.3 Distributions of wattages and nicotine concentrations



Information displayed is only from participants that reported knowing the wattage their device is typically set at (*N*=221) (left figure), or those who pay attention to the nicotine concentration of the liquids they use (*N*=366) (right figure).

CHAPTER THREE: STIMULUS EFFECTS OF PROPYLENE GLYCOL AND VEGETABLE GLYCERIN IN ELECTRONIC CIGARETTE LIQUIDS

3.1 Introduction

Electronic cigarette (EC) use has been rapidly growing worldwide. While there is ongoing debate about whether ECs serve as harm reduction devices for conventional tobacco smokers or present new public health problems, it is important to examine factors that affect their abuse liability. Currently, a major gap in our understanding of ECs is how non-nicotine liquid ingredients influence reinforcing and stimulus effects of EC aerosols.

Propylene glycol (PG) and vegetable glycerin (VG) comprise most of EC liquids (e.g. 88-96% PG and VG by weight, NJOY, 2013). Previous research suggests that ratio of PG and VG could impact the stimulus characteristics of ECs. For example, regular EC users associate PG or VG with differences in taste and sensations (e.g. 'throat hit' and 'dizziness') (Etter, 2016a; Harvanko et al., 2018). Though these studies suggest PG and VG alter stimulus effects of ECs, it is necessary to conduct a carefully controlled double-blind laboratory study to verify these effects.

Clarifying the relative effects of PG and VG would lay important ground work for future research on ECs. Regulatory efforts to decrease abuse liability of ECs would benefit from information about the influence of PG and VG on stimulus effects. Efforts to improve the efficacy of ECs as harm reduction devices for smoking cessation would also benefit from this information. The current laboratory study was conducted to examine the stimulus effects of aerosol as a function of relative concentrations of PG and VG. Based on EC user survey data (Etter, 2016a; Harvanko et al., 2018), it was

hypothesized that greater concentrations of VG would engender desirable stimulus effects (e.g. good taste, large cloud), while greater concentrations of PG would engender undesirable stimulus effects (e.g. sore throat, headache).

3.2 Methods

3.2.1 Participants

Participants were recruited from the local community using online advertisements. Prospective participants made initial contact by phone or internet and responded to a brief screening questionnaire. Participants who would potentially meet study criteria were invited into the laboratory for a screening day. Volunteers reporting use of an EC at least 20 of the past 30 days (containing nicotine the majority of the time), and no desire to reduce their EC usage, were invited to participate. Individuals were not informed of the specific inclusion/exclusion criteria for participation. Screening days were conducted on an outpatient basis at the laboratory and lasted between 2 and 3 hours on one day. Screening days involved a full discussion of the study protocol, obtaining informed consent for the screening procedure, assessment of vital statistics (i.e., heart rate, blood pressure, weight and height), pregnancy urine test for female volunteers, urine screen for psychoactive drugs that may alter the effects of nicotine, verification of recent EC use by urinary cotinine test, and completion of screening materials. Screening materials consisted of drug-use, personality, and medical history questionnaires. Participants also provided expired breath samples that were tested for the presence of alcohol (BAC) and carbon monoxide (CO; used to estimate recent tobacco use). Current EC use was verified by a timeline follow-back questionnaire (TLFB) (Sobell and Sobell, 1992). After participants completed the screening materials, results were evaluated by

the study staff and study physician, Catherine Martin, MD; individuals were excluded if they reported any condition that would increase risk for study participation, such as recent use of psychoactive drugs other than caffeine or alcohol. If approved, participants were invited to schedule the initial practice study day. Study compensation consisted of per diem payments ($50.00), monetary earnings from the Multiple Choice Procedure (described below) and a final payment ($250.00) provided upon completing all scheduled test days. Sixteen volunteers provided informed consent, and all completed the study. This study was approved by the University of Kentucky's Institutional Review Board and accorded with the Declaration of Helsinki.

3.2.2 Procedures

An EC with a refillable tank (Nautilus, Aspire, Shenzhen, China) and adjustable power supply (iStick TC100W, Eleaf, Shenzhen, China) set to 10 watts (3.7 volts, 1.4 ohm heating coil) was used for aerosol administration. Participants completed one practice day and four test days, each approximately 3 h long. Each day five liquid formulations (100/0, 75/25, 50/50, 25/75, 0/100 PG/VG) all containing 12 mg/ml nicotine were assessed in a random order that was balanced between test days and participants. The initial practice day was used to familiarize participants with study procedures and data were collected but not analyzed.

On each test day (see Table 3.1), an intake assessment comprised of the following events that occurred in a fixed order was completed within the first 30 minutes: completion of questionnaires asking about amount of tobacco smoking and EC use, hours of sleep, and drug use in the past 24 h; a field sobriety test (requiring participants to estimate the passage of 30 seconds, balance on one-leg, walk and turn, and touch their

pointer finger to their nose) that was used to detect acute drug effects and to serve as a reference for a post-day field sobriety test; consumption of a fat- and caffeine-free snack in order to standardize nutritional conditions; breath (exhaled carbon monoxide to estimate recent combustible tobacco use and blood alcohol concentration) and urine (tested to ensure non-pregnant status and for presence of common drugs of abuse) sample assays to detect use of drugs that may alter study measures; and collection of baseline control measures (i.e. cardiovascular measures, QSU-B, and VAS-SE [each described below]). In order to standardize nicotine levels and EC use prior to completing test day measures, participants then administered ten three-second puffs, with 30-second inter-puff intervals, from an EC containing liquid with 50/50 PG/VG and 12 mg/ml nicotine concentration. These puffs, as well as all subsequent puffs, were administered through a volumetric analyzer (SPA-D; Sodim, France) to measure puffing topography. Following these 10 puffs, there was a one-hour deprivation period during which participants waited in the laboratory until beginning the first choice procedure.

Each choice procedure began with completion of the QSU-B and VAS-SE control measures (described below), followed by two three-second sample puffs with 30 second inter-puff intervals from one of the liquid formulations. Participants were told to pay careful attention to the sample puffs, as they would have an opportunity to choose between an amount of money or two more puffs from the same formulation following these sample puffs. Immediately following sampling puff administration heart rate and blood pressure measurements were taken and the DSQ, QSU-B, VAS-SE, VAS-PS, and MCP (described below) were completed in a fixed-order. Then, a randomly chosen selection from the MCP was honored. If the randomly chosen selection was for two more

puffs, the participant followed computer prompts to administer two more puffs from the same formulation. If the randomly chosen selection was for money, that amount was added to the per diem compensation and provided at the end of the test day.

Five choice procedures occurred during each test day, with each of the five liquid formulations tested under double-blind conditions during one choice procedure in an order that was balanced between test days and participants. Twenty minutes separated successive choice procedures to allow any effects of the sampling puffs (and puffs administered following the MCP, if applicable) to diminish and to minimize the accumulation of nicotine across the test day. Following the last choice procedure, the participants were required to wait 30 min until being discharged from the laboratory to ensure that the opportunity to take puffs of their own EC immediately after leaving the laboratory had minimal influence on study outcomes. Participants were required to repeat the field sobriety task to assess for any residual performance effects associated with the study procedures prior to receiving daily compensation and discharge.

3.2.3 Measures

Control measures

Cardiovascular Measures (Dinamap Pro 200, General Electric). Heart rate and blood pressure were recorded using an automated blood pressure monitor.

Puff Topography (Spa-D; Sodim, France). Puff topography was recorded with a volumetric transducer and measures included total puff volume and duration.

Questionnaire of Smoking Urges - Brief (QSU-B) (Cox et al., 2001). This 10-item questionnaire focuses on nicotine withdrawal and was used to monitor nicotine

withdrawal effects on a 100-unit visual analog scale (VAS) before and after formulation sampling.

Visual Analog Scale - Smoking Effects (VAS-SE) (Blank et al., 2008). This ten-item measure was used to monitor acute nicotine effects on a 100-unit VAS scale before and after formulation sampling.

Outcome measures

Duke Sensory Questionnaire (DSQ) (Westman et al., 1996). This seven-item questionnaire asks participants to rate stimulus effects associated with smoking on a 7-point Likert scale.

Visual Analog Scale - Post Sampling (VAS-PS). This 12-item questionnaire assesses taste and other stimulus effects associated with the use of ECs using a 100-unit VAS scale. Items included: "feel stimulated," "like the effects," "want to use the electronic cigarette again," "enjoy the electronic cigarette," "crave the electronic cigarette," "get pleasure from the electronic cigarette," "produce a large vapor cloud," "experience a throat hit," "feel dry-mouth," "feel sore-throat," "enjoy the smell," and "enjoy the taste?"

Multiple Choice Procedure (MCP) (Griffiths et al., 1993). The MCP was comprised of 21 choices between two more three-second puffs of the sampled liquid formulation or an amount of money beginning at $.00 and increasing in increments of $.05 until $1.00 was reached. A randomly selected choice was honored. If two more puffs were selected on this choice, two more puffs from the same formulation were administered following *control* and *outcome* measures. If money was selected, that amount was added to compensation provided at the end of the test day. The dependent

variable on this measure was the breakpoint at which participants chose money over two more puffs.

3.2.4 Data Analysis

Mixed models were used to examine differences among liquid formulations. For control measures that were taken immediately before and after puffing bouts (e.g. the VAS-SE and QSU-B), change scores were calculated for each formulation. Since heart rate and blood pressure were taken at the beginning of each test day and following each puff bout, change scores from baseline for each test day were calculated to account for daily fluctuations in resting heart rate and blood pressure. Control measures were included to detect prototypical acute nicotine and withdrawal effects as a function of the test formulations and choice procedures. On measures taken following puffing bouts (i.e. DSQ, VAS-PS, and MCP), raw scores were analyzed. Contrasts for linear and quadratic dose-response across the formulations were used to examine main effects. Analyses were conducted using PC-SAS, version 9.3 (SAS Institute Inc., Cary, NC) and alpha was set at $p \leq 0.05$.

3.3 Results

Demographic and clinical variables are reported in Table 3.2. The majority of participants were young (25 years old) male (75%) exclusive EC users (87.5%) with a moderate level of nicotine dependence (14.8 on the mFTND). An overview of all statistical test results is shown in Table 3.3.

Control Measures

On average, each puff produced 168.13 (*SE* = 20.30) ml of aerosol and lasted 4.10 (*SE* = .30) seconds in duration. There were no significant effects of liquid formulation on duration or volume of the puffs.

Heart rate significantly decreased an average of 6.07 (*SE*=1.90) beats per minute from baseline for all of the liquid formulations (*p*s<.05), this change in heart rate did not vary significantly with formulation. There was a significant change in systolic blood pressure (SBP, Figure 3.1) (F[55]=3.67, p=.010) with post-hoc tests indicating a quadratic relationship among formulations (F[55]=12.66, p<.001), such that SBP decreased significantly more following 100/0 PG/VG (*m*=-6.55, *SE*=1.60) and 0/100 PG/VG (*m*=-4.47, *SE*=1.47) compared to 50/50 PG/VG (*m*=-6.5, *SE*=1.60).

Mixed models for QSU-B or VAS-SE items did not indicate significant effects of liquid formulation (Table 3.3).

Outcome Measures

For DSQ items, there was a significant effect of liquid formulation on "how much nicotine do you estimate was in the puffs" (F[60]=3.05, p=.023) (Figure 3.2), "what was the strength of the puffs on your tongue" (F[60]=3.98, p=.006), and "what was the strength of the puffs in your chest" (F[60]=3.52, p=.012) (Figure 3.3). Post-hoc tests indicated quadratic relationships between liquid formulation and these items, such that mixtures of PG/VG were rated more highly than PG or VG alone (e.g. right panel, Figure 3.4). The magnitude of effect, however, was small with a maximum difference of .5 units between all formulations on this five-point scale.

For VAS-PS items, significant effects of liquid formulation were indicated on "did the e-cig produce a large cloud" (F[60]=2.77, p=.035) and "did you experience a

throat hit" (F[60]=3.43, p=.014) (Figure 3.5). Post-hoc tests indicated a linear relationship on large cloud (F[60]=10.59, p=.002) (left panel, Figure 3.4) and a quadratic relationship on throat hit (F[60]=7.66, p=.008), such that throat hit was rated slightly lower on formulations containing 100% VG (36.4, SE=5.7) or 100% PG (32.4, SE=5.7) compared to formulations with 50/50% PG/VG (38.0 SE=5.7).

No effects of formulation were observed on the MCP. Notably, monetary value of these formulations was low, with the average breakpoint for all formulations being $0.04 ($SE$ = .02) (Figure 3.6).

3.4 Discussion

This is the first laboratory study of the stimulus effects of aerosols based on variations in PG and VG concentration in EC liquids. Consistent with our hypotheses, liquid formulations with more VG were associated with greater visibility of exhalant. Also, liquids with equal concentrations of PG and VG mixtures were associated with greater strength on the tongue and other common CC sensations, and smaller reductions in systolic blood pressure compared to liquids with solely PG or VG, although the magnitude of these effects were small.

Visibility of the exhalant is of interest to many EC users and has been noted as an important factor for mimicking the experience of using a conventional cigarette (CC) (Barbeau et al., 2013). Since greater concentrations of VG were associated with this effect, this information could be used to tailor ECs for those who place importance on greater "cloud" production. Past research has also shown that EC users associate throat hit with smoking cessation efficacy of the EC (Etter, 2016a), as presence of throat hit creates a greater resemblance to CC smoking (Barbeau et al., 2013). Since throat hit and

other CC inhalation sensations were associated with PG/VG mixtures (e.g. 50/50 PG/VG), incorporating both ingredients in EC liquids may be helpful for tailoring ECs to individuals desiring an experience more closely resembling that of CCs.

This study was designed to assess stimulus effects of the EC liquid formulations under controlled flavorant, nicotine, and nicotine withdrawal conditions. Given individual differences in flavor preferences, formulations devoid of flavorants were used. Plasma nicotine was not measured, but there were no differences indicated between formulations on *control* measures (i.e. VAS-SE, and QSU-B, Table 3.3). Also, average heart rate following puffing did not change as a function of liquid formulation, suggesting that nicotine delivery was not significantly different between formulations under these conditions. There was, however, an interesting quadratic relationship between formulations and SBP (Figure 3.1). Yet, interpreting this finding is difficult because nicotine delivery is typically associated with changes in heart rate rather than blood pressure (e.g. Benowitz et al., 1982). It should be noted, however, that previous research has suggested PG and VG can influence nicotine delivery (Yan and D'Ruiz, 2015; Baassiri et al., 2017). Thus, further research on the effects of these ingredients on plasma nicotine concentration is warranted.

Breakpoints on the MCP were low for each of the liquid formulations, indicating a floor effect that limits interpretation of these data. One possibility for the modest monetary value of these formulations was the omission of flavorants. Reports of 'good taste' were low following puffing (<15 on a 100-unit scale), and spontaneous reports by participants indicated dissatisfaction with the flavor. Thus, the reinforcing effects of ECs appear to be dependent on flavorants.

In a recent survey (Harvanko et al., 2018) EC users associated PG with sore throat, headache, and dizziness, and VG with good smell, cloud production, and taste. There were, however, no significant differences reported on most of these items in the present study. This may suggest that – aside from cloud production – common perceptions of PG and VG effects among experienced EC users may not be accurate. It is also possible that conditions in this study may have reduced the likelihood that PG/VG effects reported in the survey study could be detected. For example, use of a paced puffing procedure was necessary to standardize puffs across formulations, but did not likely engender puff topographies present in the natural ecology. Puff topographies used in the natural ecology may engender subjective effects associated with these ingredients that were not detectable with the standardized puffs used in this study. Also, use of certain EC parameters (e.g. wattage) may not have been optimal for detecting differences in PG/VG cue effects, and differences in these ingredients may become more apparent at different power levels. Another possible reason for these disparate results could be the context under which cues were measured; the survey study prompted participants to use unblinded and potentially biased experience with PG and VG in reporting cue effects, whereas cue effects were engendered by formulations presented under double-blind conditions in the laboratory study. In the natural ecology perceptions of PG and VG effects could be shaped by outside stimuli (e.g. peer influences) and expectation effects (e.g. preconceived notions that PG or VG are associated with certain effects). In the laboratory study, however, participants were not informed that PG and VG were being manipulated, and therefore potential biases were controlled. Another possibility is that the format of the self-report measures contributed to the discrepancy between these

studies. In the survey study participants were asked to rate how closely associated PG and VG are to several subjective effects on a 100-point slider, anchored with PG on one end, and VG on the other. In the laboratory study participants were given a 100-point slider for each subjective effect, anchored with 'not at all' on one end, and 'extremely' on the other. Lastly, it is possible that critical cue effects relevant to PG and VG in EC liquids were not comprehensively assessed. Although the subjective effect measures were carefully selected from previous research, future studies may consider using a mixed methods approach to examine stimulus effects following double-blinded presentation of formulations with varying amounts of PG and VG to examine the spectrum of potential cues produced by PG and VG in EC liquids.

3.4.1 Conclusion

These data suggest VG has a greater effect on the visibility of exhalant (i.e. cloud) compared to PG, and equal mixtures of PG/VG are better at producing inhalation sensations similar to conventional cigarettes. Neither ingredient was related to reinforcing effects (e.g. liking; Figure 3.7), but the formulations used in the current study, devoid of flavorants, had little monetary value.

Table 3.1 Laboratory Study Test Day Schedule

Time (min)	**Study Activity**	
0	Pre-session questionnaire, field sobriety test, snack provided, breath analyses, urinary analyses, pre-administration measures, heart rate and blood pressure measured	
30	10-puffs administered	
35	One-hour deprivation period	
95	Pre-administration measures	**1st choice procedure**
96	Two sample puffs administered	
97	Post-administration measures	
102	Two-more puffs administered (if applicable)	
115	Pre-administration measures	**2nd choice procedure**
116	Two sample puffs administered	
117	Post-administration measures	
122	Two-more puffs administered (if applicable)	
	…Choice procedures repeated until all five are finished…	
180	30 min waiting period	
210	Field sobriety test and participant paid and allowed to leave the laboratory	

Table 3.2 Demographic and Clinical Variables

	N=16
Age, *mean (SD)*	24.8 (3.65)
Sex, *N (%)*	
Male	12 (75.0)
Female	4 (25.0)
mFTND Score, *mean (SD)*	14.8 (3.8)
Typical electronic cigarette nicotine concentration (mg/ml), *mean (SD)*	7.13 (5.2)
Typical electronic cigarette nicotine wattage, *mean (SD)*	64.5 (33.4)
Milligrams of electronic cigarette liquid per day, *mean (SD)*	6.6 (7.5)
Years of electronic cigarette use, *mean (SD)*	2.7 (1.8)
Use of other tobacco products in the past month	
Conventional Tobacco Cigarettes, *N (%)*	2 (12.5)
Chewing Tobacco	1 (6.3)
Hookah	1 (6.3)

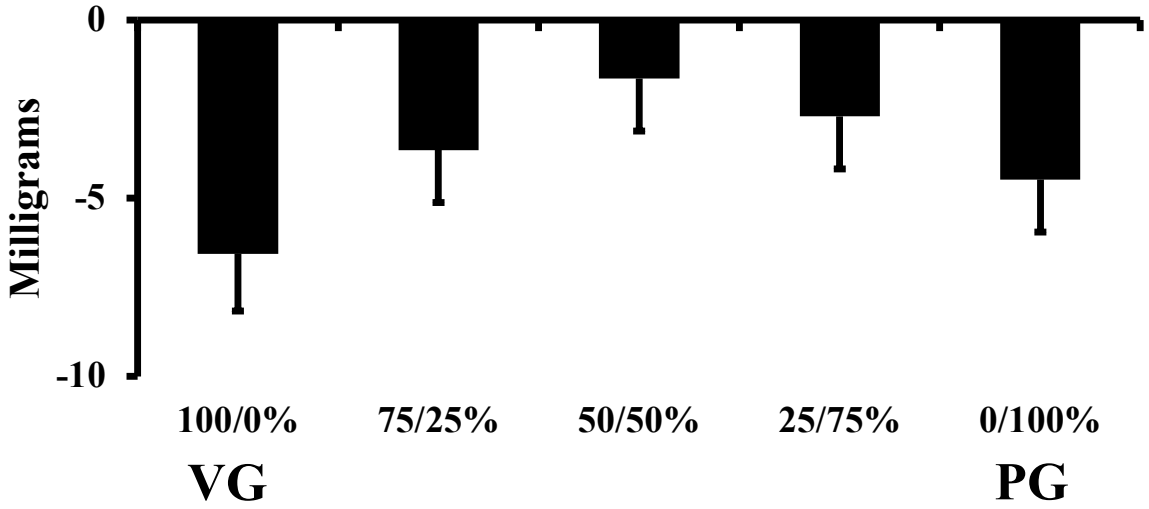
Table 3.3 Results of mixed models for all laboratory measures

		Linear	Quadratic
	F	Post-Hoc	Post-Hoc
CONTROL MEASURES			
Visual Analog Scale – Smoking Effects			
Do you feel confused?	—	—	—
Do you feel dizzy?	—	—	—
Do you feel headache?	—	—	—
Do you feel heart pounding?	—	—	—
Do you feel lightheaded?	—	—	—
Do you feel nauseous?	—	—	—
Do you feel nervous?	—	—	—
Do you feel salivation?	—	—	—
Do you feel sweaty?	—	—	—
Do you feel weak?	—	—	—
Do you feel stimulated?	—	—	—
Puff Topography			
Per Puff Volume	—	—	—
Per Puff Duration	—	—	—
Physiological Measures			
Heart rate	—	—	—
Diastolic blood pressure	—	—	—
Systolic blood pressure	**3.67***	—	**12.66****
Questionnaire of Smoking Urges - Brief			
I have a desire for an electronic cigarette right now.	—	—	—
Nothing would be better than using an electronic cigarette right now.	—	—	—
If it were possible I would probably use an electronic cigarette now.	—	—	—
I could control things better right now if I could use an electronic cigarette.	—	—	—
All I want right now is to use an electronic cigarette.	—	—	—
I have an urge for an electronic cigarette.	—	—	—
An electronic cigarette would taste good now.	—	—	—
I would do almost anything or an electronic cigarette now.	—	—	—
Using an electronic cigarette would make me less depressed.	—	—	—
I am going to use an electronic cigarette as soon as possible.	—	—	—
OUTCOME MEASURES			
Multiple Choice Procedure			

Breakpoint	—	—	—
Duke Sensory Questionnaire			
How much nicotine do you estimate was in the last puffs?	**3.05***	—	**6.20***
How similar were those puffs to your typical electronic cigarette?	—	—	—
What was the strength of the puffs on your tongue?	**3.98****	—	**9.78***
What was the strength of the puffs in your nose?	—	—	—
What was the strength of the puffs in the back of your mouth and throat?	**2.91***	—	—
What was the strength of the puffs in your windpipe?	**3.09***	—	—
What was the strength of the puffs in your chest?	**3.52***	—	**5.16***
Visual Analog Scale – Post Smoking			
Do you like the effects?	—	—	—
Do you want to use the electronic cigarette again?	—	—	—
Did you enjoy the electronic cigarette?	—	—	—
Do you crave the electronic cigarette?	—	—	—
Did the electronic cigarette produce a large vapor cloud?	**2.77***	**10.59****	—
Did you experience a throat hit?	**3.43***	—	**7.66***
Do you feel dry mouth?	—	—	—
Do you feel sore throat?	—	—	—
Did you enjoy the smell?	—	—	—
Did you enjoy the taste?	—	—	—
Did you dislike the effects?	—	—	—

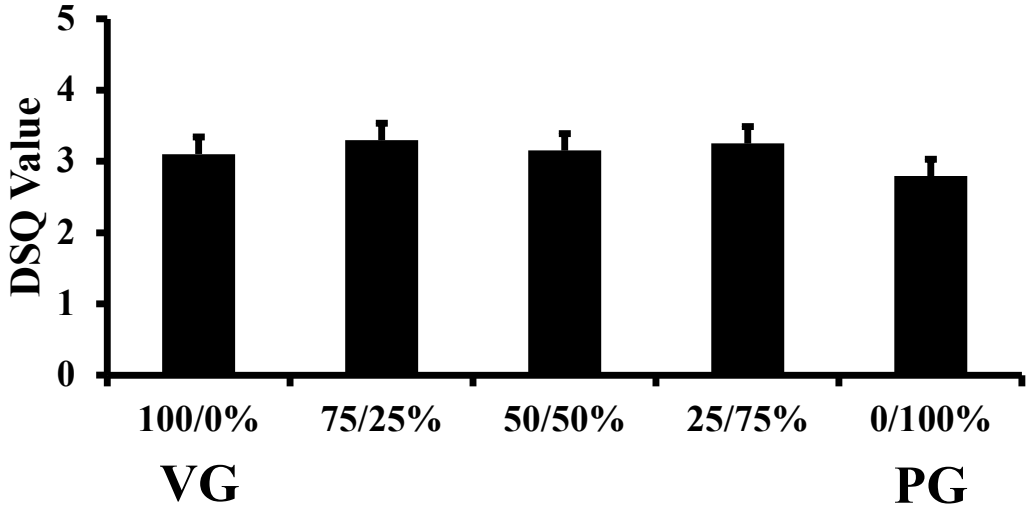
*=$p<.05$, **=$p<.01$, '—' = statistic not significant

Figure 3.1 Changes in systolic blood pressure



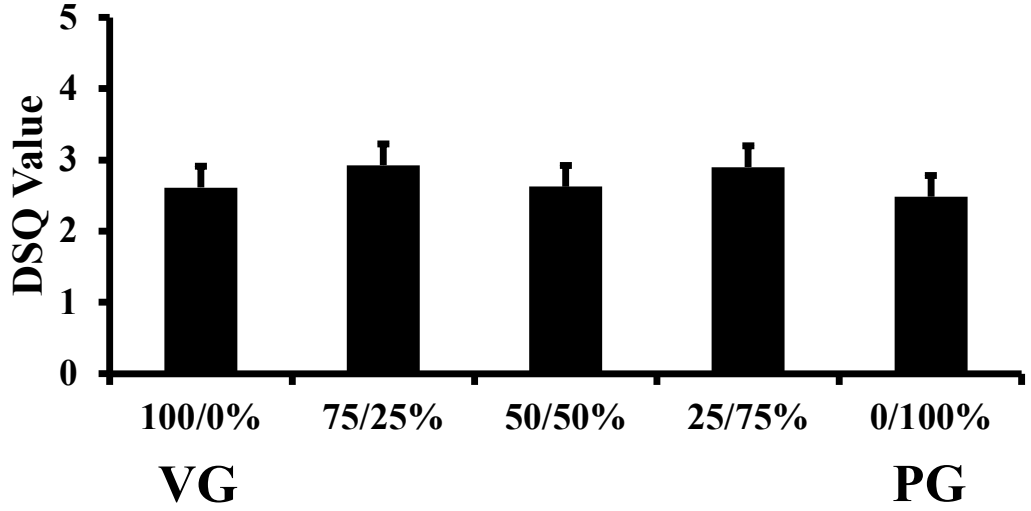
Change in systolic blood pressure from baseline to following two-puff bouts. A significant quadratic relationship between formulations was indicated (F[55]=12.66, p<.001)

Figure 3.2 Ratings of "how much nicotine do you estimate was in the last puffs?"



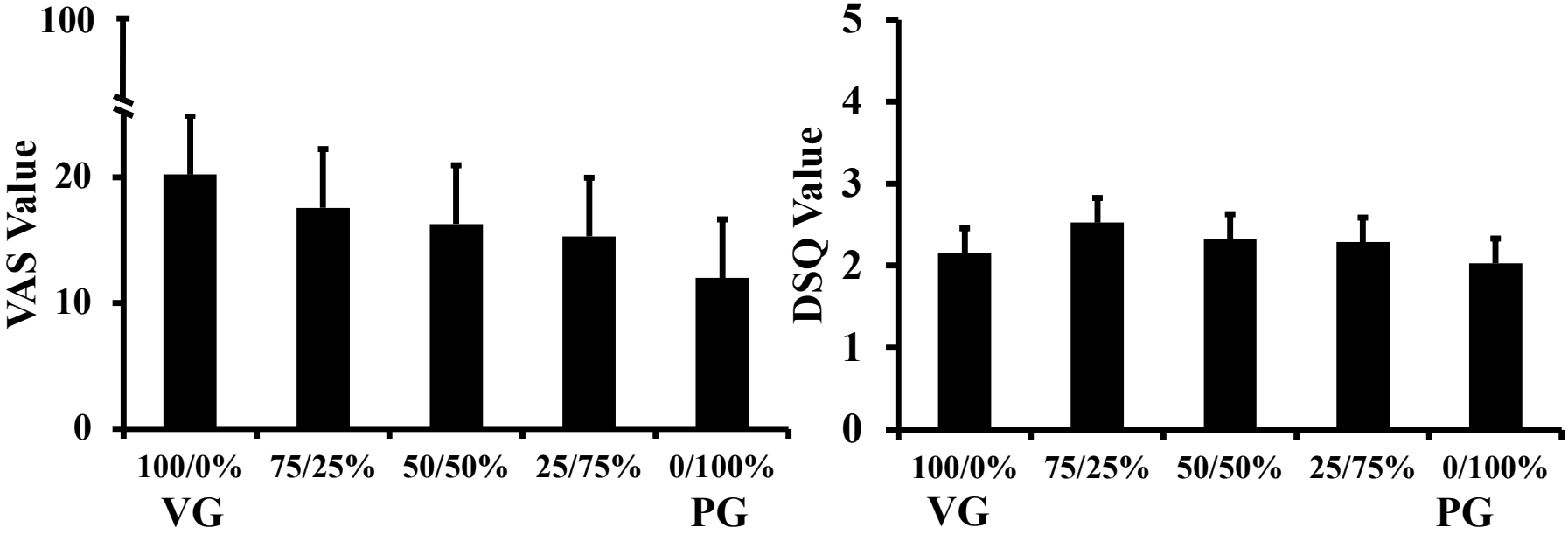
Ratings of "how much nicotine do you estimate in the last puffs" following two-puff bouts. A significant quadratic relationship between formulations was indicated (F[60]=6.2, p=.016).

Figure 3.3 Ratings of "what was the strength of the puffs in your chest?"



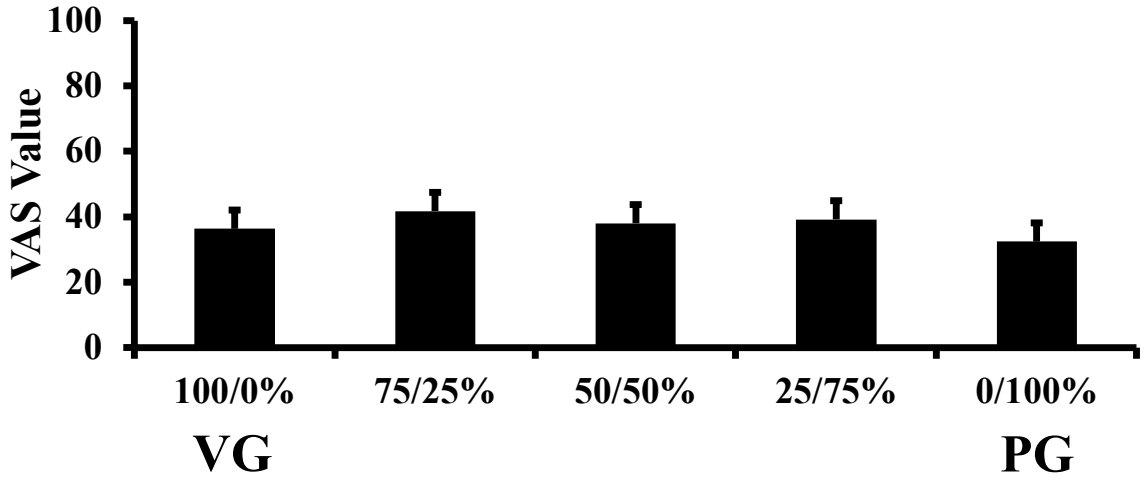
Ratings of "what was the strength of the puffs in your chest" following two-puff bouts. A significant quadratic relationship between formulations was indicated (F[60]=5.16, p=.027).

Figure 3.4 Ratings of "did the electronic cigarette produce a large cloud?" and "what was the strength of the puffs on your tongue?"



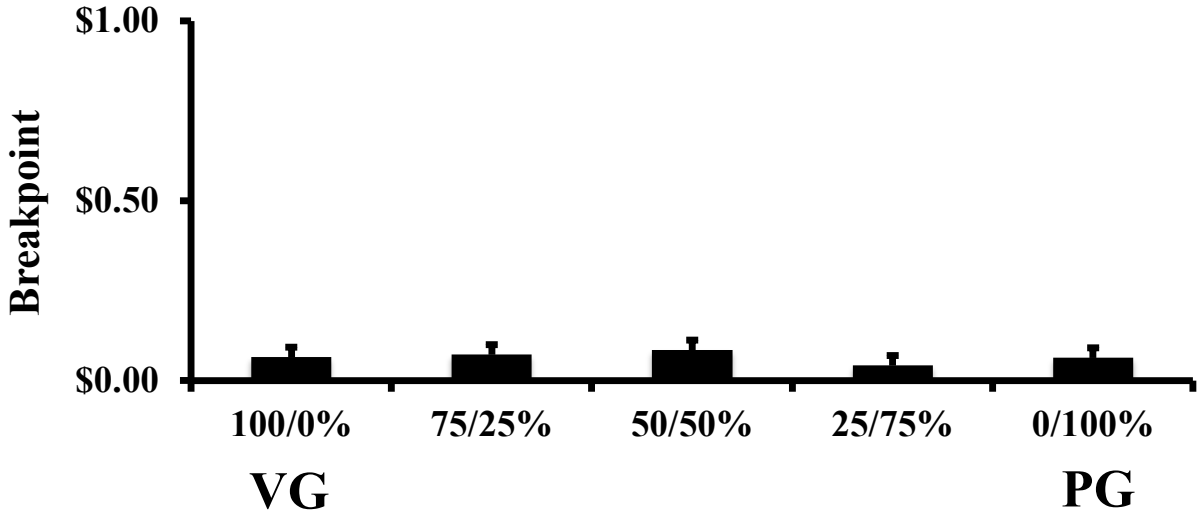
Ratings of 'did the electronic cigarette produce a large cloud' on a 100-point visual analog scale (left) and "what was the strength of the puffs on your tongue" (right). Values represent least-squares mean estimates and standard error bars derived from the mixed model. A significant main effect of liquid condition was indicated on "large cloud" (F[60]=2.77, p=.035) and post-hoc tests indicated a significant linear relationship (F[60]=10.59, p=.002). A significant main effect of liquid condition was indicated on "strength on the tongue" (F[60]=3.98, p=.006) and post-hoc tests indicated a significant quadratic relationship (F[60]=9.78, p=.003).

Figure 3.5 Ratings of "did you experience a throat hit?"



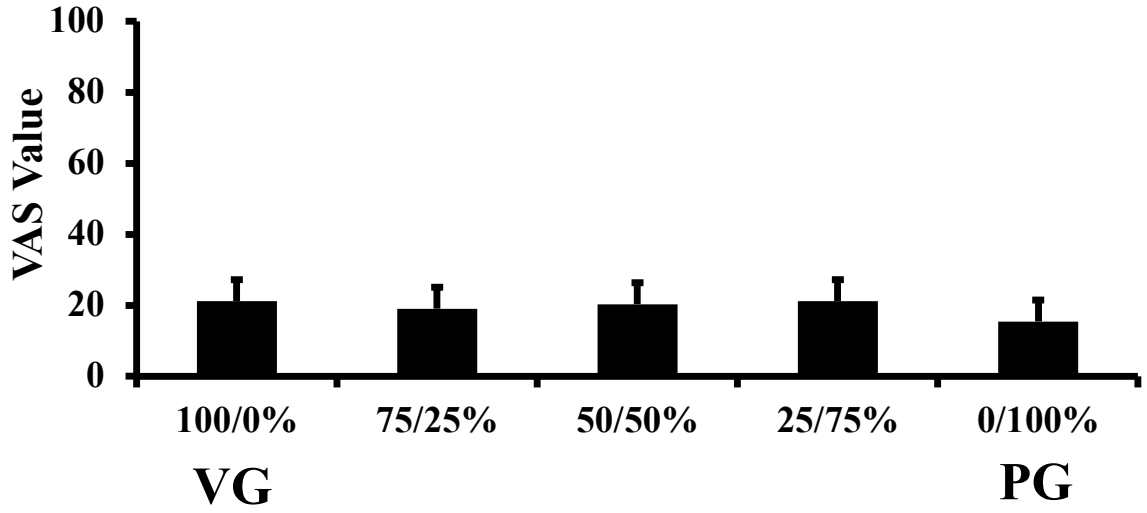
Ratings of "did you experience a throat hit" following two-puff bouts. A significant quadratic relationship between formulations was indicated (F[60]=7.66, p=.008).

Figure 3.6 Breakpoint on the Multiple-Choice Procedure



Breakpoints between money and two-more puffs, as measured by the multiple-choice procedure. There were no significant differences among liquid formulations.

Figure 3.7 Ratings of "do you like the effects?" of the puff



Ratings of "do you like the effects" following two-puff bouts. There were no significant differences among liquid formulations.

CHAPTER FOUR: OVERALL DISCUSSION

This dissertation examined the effects of PG and VG on the abuse liability of ECs by collecting self-reported perceptions of EC users in an online survey, and by using gold-standard measures of abuse liability in a laboratory study. The results of the survey indicated that EC users associate PG with undesirable effects, while VG is associated with desirable effects. With the exception of "large cloud" being associated with formulations containing greater amounts of VG and "throat hit" being more closely associated with a mixture of PG and VG (Figure 3.5), these user perceptions were not consistent with subjective effects observed in the laboratory study under controlled, double-blind conditions in the absence of taste cues. Other sensations typically associated with CCs (i.e. estimates of nicotine in the puffs [Figure 3.2], and strength of the puffs on the tongue [Figure 3.4] and in the chest [Figure 3.3]) were associated with mixtures of PG and VG, which may suggest that mixtures of PG and VG have greater liability for abuse compared to PG or VG alone among individuals who are former or current CC users. Yet, since subjective effects typically associated with abuse liability (e.g. 'liking' [Figure 3.7]) were not associated with PG or VG concentrations and of small magnitude under the limited conditions in which significant effects were observed, these data provide evidence that PG and VG have minimal impact of the reinforcing efficacy of ECs under the testing conditions in the laboratory study. In the absence of any taste cues, however, the aerosols produced by the ECs used in the laboratory study were not reinforcing according to the MCP (Figure 3.6). Due to the lack of clear reinforcing effects of the aerosols in this study, future research should examine possible

differences in reinforcing effects of PG and VG when taste cues are included in the EC aerosol conditions.

Although PG and VG did not significantly influence typical measures of liability for abuse (see Table 3.3), results of the survey and laboratory study may provide some insights on the perhaps modest influence of PG and VG liquid concentrations on liability for abuse. Subjective reports of 'large cloud' were perceived as being related to VG in the survey and positively correlated with amount of VG in the EC liquid in the laboratory study. Visibility of the exhalant may be an important effect for many EC users, and particularly individuals who are transitioning from CCs to ECs. From a smoking cessation perspective, the more closely ECs match the stimulus characteristics of CCs, the more likely they are to be effective as smoking cessation tools. Thus, because visible smoke emission is a stimulus associated with CCs, mimicking this stimulus may increase smoking cessation efficacy of ECs. Many EC users are also enthusiasts about creating large clouds (Chu et al., 2016), and among this population VG may increase the abuse liability of EC liquids.

In the laboratory study greater reports of "strength on the tongue" and other common CC smoking sensations were associated with mixtures of PG and VG as opposed to PG or VG alone, which may also have an effect on abuse liability among some EC users. Also, survey respondents did not report PG or VG being more closely related to throat hit, which is consistent with these laboratory study data. Nicotine concentration was, however, positively correlated with throat hit in the survey study. With this in mind, EC users may be able to obtain greater throat hit by optimizing PG and VG ratios, increasing liquid nicotine concentrations, or both. Though, it should be

emphasized that the effects on throat hit among PG and VG formulations in the laboratory study were modest. Nonetheless, from a smoking cessation perspective, use of mixtures of PG and VG may increase efficacy of ECs for smoking cessation among individuals placing importance on common CC sensations, or if they are trying to mimic the effects of a CC. Alternatively, abuse liability of ECs may be increased among individuals with a significant CC use history when mixtures of PG and VG are used because of its ability to increase throat hit and other CC smoking sensations. Since it could be speculated that history of CC use is an important factor when considering similarity of EC sensations to CCs, future research may wish to examine populations of never CC users compared to current or previous CC users to study the importance of these sensations between these groups.

The intention of the laboratory study was to examine the stimulus effects of EC liquids, while avoiding significant plasma nicotine accumulation, so small puffing bouts (i.e. two-puffs) were used for each formulation to avoid significant delivery of nicotine while still allowing stimulus effects not mediated by the central nervous system (CNS) to be experienced. Therefore, the current study was not designed to detect differences in nicotine delivery among PG and VG concentrations. As such, expectedly, there were no significant differences among PG and VG concentrations on control measures (i.e. prototypical nicotine effects, Table 3.3). Some research mentioned previously (Yan and D'Ruiz, 2015; Baassiri et al., 2017) has suggested that PG and VG in EC liquids would have an impact on nicotine delivery, potentially by altering nicotine content in EC aerosols. With this in mind, future studies focusing on differences in prototypical nicotine effects and plasma nicotine concentrations are warranted. For example, it is

possible future research studies using larger puffing bouts, which would engender significant plasma nicotine concentrations, may find significant differences on prototypical nicotine effects. Though the laboratory study design was not intended to induce significant effects of nicotine in the CNS, if PG and VG caused differential amount of nicotine in the aerosol, this could alter stimulus characteristics not mediated by the CNS. Past research, for example, has shown differing stimulus effects from de-nicotinized CCs paired with intravenously administered nicotine vs smoking a CC with nicotine (Westman et al., 1996), indicating that nicotine alters stimulus effects not associated with CNS activity (e.g. inhalation sensations). As such, results from the laboratory study might suggest that differences observed in CC like smoking sensations are due to differences in aerosol nicotine concentration across PG and VG formulations. Research looking directly at this possibility is, however, necessary to determine if aerosol nicotine concentration is the mechanism mediating CC like smoking sensations.

There are several possible explanations for the disparity between perceptions of PG and VG effects in the survey study and results of the laboratory study. The survey study indicates that EC parameters are utilized heterogeneously among users, and it is possible that PG and VG effects differ as a function of parameter settings. Supporting this idea, Talih and colleagues (2017) used machine puffing to demonstrate that presence of PG or VG in aerosol emissions varies depending on EC power, suggesting there would be an interacting influence of power and concentration of PG and VG in EC liquids on subjective effects. Another possibility is that amount of PG and VG in liquids is correlated with inclusion of specific flavorants, such that perceptions of PG and VG interact with effects of other flavorants. With this in mind, future research examining

ingredients of EC liquids may want to explore this possibility. Lastly, it could simply be that EC users have developed perceptions of PG and VG that are based on inaccurate anecdotal reports that have perpetuated throughout the community.

In the laboratory study the reinforcing effects of all formulations of PG and VG were minimal, such participants often chose $0.00 over two more puffs of any of the formulations (Figure 3.6). This could be because the MCP is not sensitive enough to detect the perhaps modest reinforcing effects of the ECs used under the conditions of this study. Although much previous research has shown that the MCP is an effective way to measure the reinforcing effects of drugs of abuse in a laboratory setting (e.g. Griffiths et al., 1993, Griffiths et al., 1996, Vansickel et al., 2012), the MCP has not always been effective at detecting reinforcing effects of drugs with well-known abuse liability (e.g. Rush et al., 1999). It is also possible that a lack of a strong signal on the MCP in the laboratory study was due to a lack of flavoring in the EC liquids. In support of this, many participants in the laboratory study spontaneously reported that the taste of these formulations was not desirable and, as indicated in the survey study, most EC users rate taste as the most important factor when selecting EC liquids. Thus, these results may further suggest that the addition of flavorants in liquids is a major contributor to the reinforcing effects of EC liquids. As of yet, no other published research has examined the reinforcing effects of unflavored liquids in ECs. As such, though there are many parameters that may have affected the reinforcing effects of the liquids in this study (e.g. the relatively short period of nicotine deprivation, the EC parameters used), further research could begin evaluating the reinforcing effects of flavorants added to EC liquids.

It could be speculated that utilizing liquids with added flavorants may have been a more effective approach to measuring the effects of PG and VG in the laboratory study. Yet, while including flavorants into the liquids may have increased reinforcing effects, it would have hampered interpretation of the study results for two reasons: 1) participants would likely have had different preferences for flavorings, and addition of one kind of flavor profile may have only increased reinforcing effects of the EC liquids for some participants – or potentially decreased reinforcing effects for others – and 2) flavorants may interact with PG and VG, and therefore obfuscate the reinforcing effects of PG and VG, which is supported by previous research demonstrating that flavorants can modulate the sensory effects of PG and VG (Rao et al., 2017). Though the addition of flavorants may not be optimal for a controlled study, future research looking to study reinforcing effects of PG and VG may benefit from developing a more acceptable aerosol than that used in this laboratory study. Aside from flavoring, since previous research has shown that reinforcing effects of nicotine are positively correlated with previous cigarette consumption (i.e. nicotine deprivation; Rose et al., 1984), using a longer deprivation period than the current study (i.e. 1 h) would also likely increase the reinforcing effects of EC liquids in a laboratory study. In addition to recency of previous EC use, availability of the next sample puffs may have reduced reinforcing effects of the liquids in this study, and therefore extending periods between bouts (i.e. > 20 min) might increase reinforcing effects of puffs in future studies. Lastly, puffing procedures in the current study were controlled to standardize dosage between formulations and participants. Constrained puffing behavior, however, may have engendered lesser reinforcing effects of the EC compared to an ad-lib puffing procedure, and therefore future studies may wish to

incorporate ad-lib puffing procedure when attempting to measure reinforcing effects of ECs.

In the context of this dissertation, the survey study was conducted primarily to provide insight on EC users' perceptions of PG and VG, and to determine what parameters (e.g. liquid nicotine concentration and wattage levels) are preferred by regular EC users. Unexpected, yet interesting, findings from this survey were the proportion of individuals who indicated not attending to common EC parameters, and the variability in parameter settings. Only 57.7% of individuals reported knowing the wattage of their device, and only 70.1% reported knowing the nicotine concentration of the liquids they typically use. Even still, among those who reported these parameters, there is a wide distribution of settings (Figure 2.3). These data underscore the challenges researchers face when attempting to identify devices and settings for use in laboratory studies that will produce results that are generalizable to the natural ecology. Recently the National Institute on Drug Abuse began offering the Standardized Research Electronic Cigarette (SREC) in an attempt to standardize ECs used in research. This device functions at a power level of 9 watts, and is offered with unflavored or tobacco flavored liquids containing 0 or 15 mg/ml nicotine concentration and 50/50% PG/VG. Use of this device in research and interpretation of results generated with it, however, must be done cautiously. Since it is known that EC parameters are used at many different settings, it is possible that results produced with the SREC will have limited generality. Use of the unflavored SREC liquid, for example, may be problematic because – as data in the laboratory study conducted here demonstrate – unflavored liquids may not be reinforcing under certain conditions. Lastly, since taste was indicated as the most important factor

when selecting EC liquids, availability of only one type of flavored liquid (i.e. tobacco flavor) may limit reinforcing efficacy of the SREC to certain populations. As such, future research may want to examine the reinforcing efficacy of the SREC in comparison to other ECs, and particularly its comparison to research participants' preferred ECs.

In conclusion, the results of this dissertation inform future research by demonstrating perceptions of PG and VG among the EC using community and testing the effects of PG and VG in a carefully controlled laboratory study. Future research on ECs should be mindful that, while PG and VG may not have significant effects on the abuse liability of ECs in the absence of flavorants, these ingredients can cause significant differences on several stimulus effects, which should be accounted for when selecting liquids for research. Also, future research efforts should note that omission of flavorants in EC liquids may reduce reinforcing effects of ECs, such that measures of these effects may not produce generalizable data. Lastly, PG and VG may not be an important regulatory target from an abuse liability perspective because they did not significantly differ on typical abuse liability measures in the laboratory study, however, future research will be required to more comprehensively study PG and VG among different populations and among different EC settings.

References

ASH. (1998). *Tobacco explained : The truth about the tobacco industry ... In its own words.* ASH, San Francisco, United States.

Audrain-McGovern, J., Strasser, A. A., & Wileyto, E. P. (2016). The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. *Drug Alcohol Depend, 166,* 263-267. doi:10.1016/j.drugalcdep.2016.06.030

Baassiri, M., Talih, S., Salman, R., Karaoghlanian, N., Saleh, R., Hage, R. E., . . . Shihadeh, A. (2017). Clouds and "throat hit": Effects of liquid composition on nicotine emissions and physical characteristics of electronic cigarette aerosols. *Aerosol Sci Technol.* doi:10.1080/02786826.2017.1341040

Barbeau, A.M., Burda, J., & Siegel, M., 2013. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: A qualitative approach. *Addiction Sci Clin Pract,* 8(1), 1.

Bell, S. L., Taylor, R. C., Singleton, E. G., Henningfield, J. E., & Heishman, S. J. (1999). Smoking after nicotine deprivation enhances cognitive performance and decreases tobacco craving in drug abusers. *Nicotine Tob Res*, *1*(1), 45-52. doi:10.1080/14622299050011141

Benowitz, N.L., Jacob, P., Jones, R.T., & Rosenberg, J. (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *J Pharmacol Exp Ther*, 221(2), 368-72.

Blank, M.D., Sams, C., Weaver, M.F., & Eissenberg, T. (2008). Nicotine delivery, cardiovascular profile, and subjective effects of an oral tobacco product for smokers. *Nicotine Tob Res*, *10*(3), 417-21. doi:10.1080/14622200801901880

Bullen, C., McRobbie, H., Thornley, S., Glover, M., Lin, R., & Laugesen, M. (2010). Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: Randomised cross-over trial. *Tob Control*, *19*(2), 98-103.

Chu, K. H., Allem, J. P., Cruz, T. B., & Unger, J. B. (2016). Vaping on instagram: Cloud chasing, hand checks and product placement. *Tob Control*, *26*(5), 575-578. doi:10.1136/tobaccocontrol-2016-053052

Cobb CO, Hendricks PS, Eissenberg T. (2015). Electronic cigarettes and nicotine dependence: Evolving products, evolving problems. *BMC Med*, *13*(1). doi:10.1186/s12916-015-0355-y

Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (qsu-brief) in laboratory and clinical settings. *Nicotine Tob Res*, *3*(1), 7-16.

Dawkins, L., & Corcoran, O. (2014). Acute electronic cigarette use: Nicotine delivery and subjective effects in regular users. *Psychopharmacology*, *231*(2), 401-407.

Dawkins, L. E., Kimber, C. F., Doig, M., Feyerabend, C., & Corcoran, O. (2016). Self-titration by experienced e-cigarette users: Blood nicotine delivery and subjective effects. *Psychopharmacology*, *233*(15-16), 2933-41. doi:10.1007/s00213-016-4338-2

Evans, S. E., & Hoffman, A. C. (2014). Electronic cigarettes: Abuse liability, topography and subjective effects. *Tob Control*, *23*(suppl 2), ii23-ii29.

Etter, J. -F. (2016a). Throat hit in users of the electronic cigarette: An exploratory study. *Psychol Addict Behav*, *30*(1), 93.

Etter J. (2016b). Characteristics of users and usage of different types of electronic cigarettes: Findings from an online survey. *Addiction*, *111*(4). doi: 10.1111/add.13240

Etter, J. F., & Bugey, A. (2017). E-cigarette liquids: Constancy of content across batches and accuracy of labeling. *Addict Behav*, *73*, 137-143. doi:10.1016/j.addbeh.2017.05.012

Farsalinos KE, Romagna G, Tsiapras D, et al. (2013) Impact of flavour variability on electronic cigarette use experience: An internet survey. *Int J Environ Res Public Health*, *10*(12). doi: 10.3390/ijerph10127272

Farsalinos KE, Romagna G, Tsiapras D, et al. (2014a) Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*, *11*(4). doi: 10.3390/ijerph110404356

Farsalinos KE, Spyrou A, Tsimopoulou K, et al. (2014b) Nicotine absorption from electronic cigarette use: Comparison between first and new-generation devices. *Scientific Reports*, *4*(4133). doi:10.1038/srep04133

Farsalinos, K. E., Voudris, V., & Poulas, K. (2015). E-cigarettes generate high levels of aldehydes only in dry puff conditions. *Addiction. 110*(8), 1352-1356. doi: 10.1111/add.12942.

Foulds J, Veldheer S, Yingst, et al. (2015) Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking e-cigarette users. *Nicotine Tob Res*, *17*(2). doi: 10.1093/ntr/ntu204

Geiss, O., Bianchi, I., & Barrero-Moreno, J. (2016). Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. *Int J Hyg Environ Health*, *219*(3), 268-277. doi: 10.1016/j.ijheh.2016.01.004

Gillman, I. G., Kistler, K. A., Stewart, E. W., & Paolantonio, A. R. (2016). Effect of variable power levels on the yield of total aerosol mass and formation of aldehydes in e-cigarette aerosols. *Regul Toxicol Pharmacol*, *75*, 58-65. doi:10.1016/j.yrtph.2015.12.019

Griffiths, R. R., Ator, N. A., Roache, J. D., & Lamb, R. J. (1987). Abuse liability of triazolam: Experimental measurements in animals and humans. *Psychopharmacol Ser*, *3*, 83-7.

Griffiths, R. R., JR Troisi, I. I., Silvermian, K., & Miumford, G. K. (1993). Multiple-choice procedure: An efficient approach for investigating drug reinforcement in humans. *Behav Pharmacol*, *4*(1), 3-14.

Griffiths, R. R., Rush, C. R., & Puhala, K. A. (1996). Validation of the multiple-choice procedure for investigating drug reinforcement in humans. *Exp Clin Psychopharmacol*, *4*(1), 97-106.

Griffiths, R. R., Bigelow, G. E., & Ator, N. A. (2003). Principles of initial experimental drug abuse liability assessment in humans. *Drug Alcohol Depend*, *70*(3), S41- S54. doi:10.1016/s0376-8716(03)00098-x

Harvanko, A. M., Martin, C. A., Kryscio, R. J., Stoops, W. W., Lile, J. A., & Kelly, T. H. (2017). A prototypical first-generation electronic cigarette does not reduce reports of tobacco urges or withdrawal symptoms among cigarette smokers. *J Addict*, *2017*, 6748948. doi:10.1155/2017/6748948

Harvanko, A. M., McCubbin, A. K., Ashford, K. B., Kelly, T.H. (2018). Electronic cigarette liquid and device parameters and aerosol characteristics: A survey of regular users. *Addict Behav*, *84*, 201-206. doi:10.1016/j.addbeh.2018.04.009

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry*, *43*(3), 289-294.

Jensen, R. P., Luo, W., Pankow, J. F., Strongin, R. M., & Peyton, D. H. (2015). Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*, *2015*(372), 392-394.

Kangertech. Retrieved October 10, 2017(a), from https://web.archive.org/web/20151105061643/http://www.kangeronline.com:80/collections/mods, 2015.

Kangertech. Retrieved October 10, 2017(b), from https://web.archive.org/web/20161118214918/http://kangeronline.com:80/collections/mods, 2017.

Kosmider, L., Sobczak, A., Fik, M., Knysak, J., Zaciera, M., Kurek, J., & Goniewicz, M. L. (2014). Carbonyl compounds in electronic cigarette vapors: Effects of nicotine solvent and battery output voltage. *Nicotine Tob Res*, *16*(10), 1319-1326.

Lik, H. U.S. Patent 7832410B2, 2005

Lopez, A. A., Hiler, M. M., Soule, E. K., Ramôa, C. P., Karaoghlanian, N. V., Lipato, T., . . . Eissenberg, T. (2016). Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: A preliminary report. *Nicotine Tob Res*, *18*(5), 720-723. doi:10.1093/ntr/ntv182

Marynak, K. L., Gammon, D. G., Rogers, T., Coats, E. M., Singh, T., & King, B. A. (2017). Sales of nicotine-containing electronic cigarette products: United states, 2015. *Am J Public Health*, *107*(5), 702-705. doi:10.2105/AJPH.2017.303660

McCabe, S. E., West, B. T., Veliz, P., & Boyd, C. J. (2017). E-cigarette use, cigarette smoking, dual use, and problem behaviors among U.S. Adolescents: Results from a national survey. *J Adolesc Health*, *61*(2), 155-162. doi:10.1016/j.jadohealth.2017.02.004

NJoy LLC, U.S. patent 20140345635A1, 2013.

Panlilio, L. V., & Goldberg, S. R. (2007). Self-administration of drugs in animals and humans as a model and an investigative tool. *Addiction*, *102*(12), 1863-70. doi:10.1111/j.1360-0443.2007.02011.x

Perkins, K. A., Sexton, J. E., Reynolds, W. A., Grobe, J. E., Fonte, C., & Stiller, R. L. (1994). Comparison of acute subjective and heart rate effects of nicotine intake via tobacco smoking versus nasal spray. *Pharmacol Biochem Behav*, *47*(2), 295-299.

Ramôa, C. P., Hiler, M. M., Spindle, T. R., Lopez, A. A., Karaoghlanian, N., Lipato, T., . . . Eissenberg, T. (2015). Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: A preliminary report. *Tob Control*, *25*(e1). doi: 10.1136/tobaccocontrol-2015-052447

Rao, P. D., Husile, N., Strasser, A. A., & Wise, P. M. (2017). Pilot experiment: The effect of added flavorants on the taste and pleasantness of mixtures of glycerol and propylene glycol. *Chemosens Percept*, 1-9. doi:10.1007/s12078-017-9231-9

Rudy AK, Leventhal AM, Goldenson NI, et al. (2017). Assessing electronic cigarette effects and regulatory impact: Challenges with user self-reported device power. *Drug Alcohol Depend*, *179*. doi:10.1016/j.drugalcdep. *07*(31)

Rush, C. R., Baker, R. W., & Wright, K. (1999). Acute physiological and behavioral effects of oral cocaine in humans: A dose-response analysis. *Drug Alcohol Depend*, *55*(1-2), 1-12.

Shihadeh, A., & Eissenberg, T. (2015). Electronic cigarette effectiveness and abuse liability: Predicting and regulating nicotine flux. *Nicotine Tob Res*, *17*(2), 158 162. doi: 10.1093/ntr/ntu175

Sobell, L. C., & Sobell, M. B. (1992). Timeline follow-back. In *Measuring alcohol consumption* (pp. 41-72). Springer.

St Helen, G., Dempsey, D. A., Havel, C. M., Jacob, P., & Benowitz, N. L. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. *Drug Alcohol Depend*, *178*, 391-398. doi:10.1016/j.drugalcdep.2017.05.042

Stolerman, I. P., & Jarvis, M. J. (1995). The scientific case that nicotine is addictive. *Psychopharmacol*, *117*(1), 2-10; discussion 14-20.

Talih, S., Balhas, Z., Eissenberg, T., Salman, R., Karaoghlanian, N., El Hellani, A., . . . Shihadeh, A. (2014). Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: Measurements and model predictions. *Nicotine Tob Res*, *17*(2), 150-157.

Talih, S., Balhas, Z., Salman, R., Karaoghlanian, N., & Shihadeh, A. (2016a). "Direct dripping": A high-temperature, high-formaldehyde emission electronic cigarette use method. *Nicotine Tob Res*, *18*(4), 453-459. doi:10.1093/ntr/ntv080

Talih S, Balhas Z, Salman R, et al. (2016b). Transport phenomena governing nicotine emissions from electronic cigarettes: Model formulation and experimental investigation. *Aerosol Sci Technol, 51*(1). doi:10.1080/02786826.2016.1257853

Talih, S., Salman, R., Karaoghlanian, N., El-Hellani, A., Saliba, N., Eissenberg, T., & Shihadeh, A. (2017). "Juice monsters": Sub-Ohm vaping and toxic volatile aldehyde emissions. *Chem Res Toxicol*, *30*(10), 1791-1793. doi:10.1021/acs.chemrestox.7b00212

Temple JR, Shorey RC, Lu Y, et al. (2017). E-cigarette use of young adults motivations and associations with combustible cigarette alcohol, marijuana, and other illicit drugs. *Am J Addict*, 2017;26:4. doi: 10.1111/ajad.12530

Vansickel, A. R., Cobb, C. O., Weaver, M. F., & Eissenberg, T. E. (2010). A clinical laboratory model for evaluating the acute effects of electronic cigarettes: Nicotine delivery profile

and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev*, *19*(8), 1945-1953.

Vansickel, A. R., Weaver, M. F., & Eissenberg, T. (2012). Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction*, *107*(8), 1493-1500.

Wagener TL, Floyd EL, Stepanov I, et al. (2017) Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control*, *26*(e1). doi:10.1136/tobaccocontrol-2016-053041

Westman, E.C., Behm, F.M., & Rose, J.E., (1996). Dissociating the nicotine and airway sensory effects of smoking. *Pharmacol Biochem Behav*, *53*(2), 309-15.

Yan, X. S., & D'Ruiz, C. (2015). Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regul Toxicol Pharmacol*, *71*(1), 24-34. doi:10.1016/j.yrtph.2014.11.004

Zhu, S. -H., Sun, J. Y., Bonnevie, E., Cummins, S. E., Gamst, A., Yin, L., & Lee, M. (2014). Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control*, *23*(suppl 3), iii3-iii9. doi:10.1136/tobaccocontrol-2014-05167

CURRICULUM VITAE

Arit Michael Harvanko

Education

B.A. Psychology, Metropolitan State University. Saint Paul, Minnesota. 2011.

M.S. Behavioral Neuroscience and Psychopharmacology, University of Kentucky. Lexington, Kentucky, 2015

Work Experience

- Assistant Audio Engineer, 2005-2008
  Maud Moon Weyerhaeuser Studio at Minnesota Public Radio
  Saint Paul, Minnesota

- Psychology Intern, 2008-2009
  Blue Iris Therapy
  Richfield, Minnesota

- Lab Assistant, 2009-2010
  Psychology Lab, Metropolitan State University
  Saint Paul, Minnesota

- Research Assistant, 2010-2012
  Impulse Control Disorders Clinic, University of Minnesota
  Minneapolis, Minnesota

- Research Assistant, 2012-2013
  Department of Psychiatry, University of Minnesota
  Minneapolis, Minnesota

- Graduate Student, 2013-2018
  Behavioral Neuroscience & Psychopharmacology, University of Kentucky
  Lexington, Kentucky

Peer-reviewed Publications

Harvanko AM, Odlaug BL, Schreiber LR, Grant JE. Cognitive task performance and frequency of alcohol usage in young adults. *Journal of Addiction Medicine.* 2012 Jun;6(2):106-11.

Grant JE, Schreiber LN, **Harvanko AM**. The neurobiology of addiction. In Addiction Syndrome Handbook (ed. Shaffer H), *American Psychological Association Press*. 2012.

Odlaug BL, SR Chamberlain, **AM Harvanko**, BA, JE Grant, Age at Onset in Trichotillomania:Clinical Variables and Neurocognitive Performance. *The Primary Care Companion for CNS Disorders*. 2012; 14(4).

Odlaug BL, Lust K, Schreiber LR, Christenson G, Derbyshire K, **Harvanko A**, Golden D, Grant JE. Compulsive sexual behavior in young adults. *Annals of Clinical Psychiatry*. 2013 Aug;25(3):193-200.

Harvanko AM, Lust K, Odlaug BL, Schreiber LR, Derbyshire K, Christenson G, Grant JE. Prevalence and characteristics of compulsive buying in college students. *Psychiatry Research.* 2013 Dec 30;210(3):1079-85.

Harvanko AM, Schreiber LR, Grant JE. Prediction of alcohol and gambling problems in young adults by using a measure of decision making. *Journal of Addiction Medicine*. 2013 Sep-Oct;7(5):314-9.

Harvanko, AM, Derbyshire, KL, Schreiber, LR, & Grant, JE. Sleepiness and cognition in young adults who gamble and use alcohol. *Journal of Behavioral Addictions,* 2014 3(3), 166-172.

Harvanko, AM, Derbyshire, KL, Schreiber, L, & Grant, JE. The effect of self-regulated caffeine use on cognition in young adults. *Human Psychopharmacology: Clinical and Experimental,* 2015 30(2), 123-130.

Harvanko AM, Martin CA, Lile JA, Kryscio RJ, Kelly TH. Individual Differences in the Behavioral Effects of d-Amphetamine: Dimensions of Impulsivity. *Experimental and Clinical Psychopharmacology.* 2016 24(6), 436-446.

Harvanko AM, Martin CA, Kryscio RJ, Stoops WW, Lile, JA, Kelly TH. A prototypical first-generation electronic cigarette does not reduce reports of tobacco urges or withdrawal symptoms among cigarette smokers. *Journal of Addiction*, 2017.

Kelly TH, **Harvanko AM**, Pierce ME, Rayapati AO, Martin CA. A Biological/Genetic Perspective: The Addicted Brain. In Adolescent Substance Abuse (ed. Leukefeld CG, Gullota TP, Staton-Tindall M), *Springer, Boston, MA. In press.*

Harvanko AM, McCubbin A, Ashford K, Kelly TH. Electronic cigarette liquid and device parameters and aerosol characteristics: A survey of regular users. *Addictive Behaviors. In press.*

In review

Harvanko AM, Strickland JC, Slone S, Shelton B, Reynolds BA. Dimensions of Impulsive Behavior: Predicting Contingency Management Treatment Outcomes for Adolescent Smokers.

Harvanko AM, Slone S, Shelton B, Dallery J, Fields S, Thornberry T, Reynolds BA. Web-Based Contingency Management for Adolescent Tobacco Smokers: A Clinical Trial.

Harvanko AM, Kryscio R, Martin CA, Kelly TH. Stimulus Effects of Propylene Glycol and Vegetable Glycerin in Electronic Cigarette Liquids.