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THE BEHAVIORAL EFFECTS OF FIRST-GENERATION ELECTRONIC CIGARETTES AFTER 24-HOUR TOBACCO DEPRIVATION

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THESIS

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ABSTRACT OF THESIS

THE BEHAVIORAL EFFECTS OF FIRST-GENERATION ELECTRONIC CIGARETTES AFTER 24-HOUR TOBACCO DEPRIVATION

Little is currently known about the ability of electronic cigarettes to manage tobacco withdrawal symptoms and their abuse liability. In the current study eight conventional cigarette smokers completed nine within-subject study sessions. In the first session participants practiced using an electronic cigarette containing 16 mg/ml of nicotine over six 10-puff bouts. Remaining study sessions were comprised of four two-day blocks (one for each condition), which assessed measures of tobacco withdrawal symptoms and abuse liability following unrestricted cigarette smoking and 24-hour tobacco deprivation. Study conditions included an electronic cigarette with 0, 8, or 16 mg/ml nicotine concentrations, or preferred brand of conventional cigarette. Following 24-hours of tobacco deprivation, smoking conventional cigarettes ameliorated many of the self-report and physiological symptoms (decreased heart rate) associated with tobacco deprivation, while no attenuation of withdrawal symptoms was indicated following using electronic cigarettes, independent of nicotine dose. On abuse liability measures there were no significant changes following using an electronic cigarette (regardless of nicotine concentration), while conventional cigarettes engendered significant changes on abuse liability measures. Within the conditions of this study, first-generation electronic cigarettes had no measurable efficacy in ameliorating tobacco withdrawal symptoms and a reduced abuse liability compared to conventional tobacco cigarettes.

KEYWORDS: Abuse liability, smoking, tobacco cessation, nicotine, withdrawal

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CHAPTER ONE: INTRODUCTION TO ELECTRONIC CIGARETTES

History and Definition

For decades attempts have been made to develop a nicotine-delivery device that provides stimuli similar to that of a tobacco cigarette without the negative aspects of inhaling tobacco smoke. One of the earliest examples of such an attempt can be found in a patent filed in 1963 (Gilbert, 1965), which proposed a device that could "provide a safe and harmless means for and method of smoking by replacing burning tobacco and paper with heated, moist, flavored air." Despite this patent, no serious attempt to manufacture and distribute such a device was made. It was not until years later that trials began on devices that delivered nicotine via inhalation. In 1979, Jacobson and colleagues (1979) published data demonstrating that serum nicotine levels comparable to those delivered by conventional tobacco cigarettes (CC) could be obtained by using a "non-combustible cigarette." This device did not use combustion or electricity but rather passive diffusion of nicotine, embedded in filter paper, into the air as the user inhaled (Dunworth, 2014). For a short while this device was manufactured and distributed under the name "Favor," but ultimately failed due to a short shelf life caused by rapid degradation of nicotine into a bitter tasting metabolite, cotinine (Dunworth, 2014). During the 1980's the major tobacco manufacturer R.J. Reynolds was attempting to develop a CC alternative. While R.J. Reynolds filed numerous patents that outlined devices practically indistinguishable from current EC's (e.g. Brooks, Roberts, and Simmons, 1990), no major attempts to distribute and manufacture such a device are documented. The invention of the modern EC has been attributed to Chinese pharmacist Hon Lik, who filed a patent in 2004 for a "flameless electronic atomizing cigarette" (Lik, 2006). This patent outlines an

electronically powered device that vaporizes a mixture containing, among other things, nicotine, glycerol, propylene glycol, and water with an electro-thermal vaporization nozzle. Most modern EC's still adhere to these basic ingredients and mechanics.

Although there are similar mechanics and ingredients between EC's, there are many variations in modern EC's that must be identified when discussing EC's. As of January 2014, it was estimated that there were at least 466 different brands of electronic cigarettes and 7,764 different flavors (Zhu et al., 2014). Amidst this large variety of options, three separable categories of EC's have emerged: first-, second-, and third-generation EC's (Zhu et al., 2014). First generation EC's, colloquially referred to as "cig-a-likes," are similar to CC's in appearance and have relatively low-capacity batteries, non-refillable liquid cartridges, few (if any) variable settings, and operate at lower wattages. First generation EC's typically come in disposable (the entire device is discarded once the battery has been depleted or the liquid is gone) or rechargeable (non-refillable liquid cartridges and the battery can be recharged) variants. Second-generation devices, also known as "eGo" devices, are relatively larger than first-generation devices and typically have larger rechargeable batteries, refillable liquid tanks, and some user adjustable parameters (e.g. variable voltage). Third-generation devices, also called "mods," typically have many user-customizable parameters (e.g. voltage or wattage) and configurations (e.g. different types of tanks or batteries), and some variants can operate at power levels of 100 watts or more.

Prevalence of Electronic Cigarette Use

Since the introduction of the modern EC about a decade ago, EC use (vaping) has been quickly increasing worldwide. In the United Kingdom, EC use more than doubled

(from 2.7% to 6.7%) between 2010 and 2012 (Dockrell et al., 2013). Among CC smokers in the Czech Republic in 2012, 50% had tried EC's, while 18.3% used EC's regularly (Kralikova et al., 2013), with 23.5% having ever used an EC and 8.2% having used an EC in the past 30 days (Goniewicz and Zielinska-Danch, 2012). Among men in Switzerland between 2010 and 2013, despite a ban on sale of nicotine containing EC's, 4.9% had used an EC in the last 12-months (Douptcheva et al., 2013). Among CC smokers in the United States, United Kingdom, Canada, and Australia between 2010 and 2011, 7.6% had tried EC's, while 2.9% were current users (Adkison et al., 2013). In the United States the percentage of individuals who were aware of EC's doubled (from 16.4% to 32.2%) between 2009 and 2010, while the percentage of individuals who had tried EC's quadrupled (from 0.6% to 2.7%) between 2009 and 2010 (Regan et al., 2013). Among young-adults (ages 18-25 years) in the United States who had reported some cigarette use (at least once per month), past-month EC use had increased from 6% in 2009-2010 to 41% in 2013 (Ramo, Young-Wolff, and Prochaska, 2015). This literature yields widely disparate prevalence estimates of EC use, which likely reflects the rapid growth of EC use by region and time. Nonetheless, there is converging evidence for a steadily increasing rate of EC use, which underscores the need for further information on the behavioral effects of these devices.

Electronic Cigarettes and Tobacco Withdrawal Symptoms

Although the health effects of EC's have not been fully characterized, leaving questions about potentially negative effects on the users health (e.g. Goniewicz et al., 2014), it has been argued that EC's could be used as a harm reduction tool for current CC smokers (for review see Farsalinos and Polosa, 2014). Although evidence showing

efficacy of EC's as smoking cessation devices is limited, a recent meta-analysis has shown that EC use is associated with a reduction in CC smoking (Rahman et al., 2015). As a smoking cessation tool, EC's might be able to diminish CC smoking withdrawal symptoms and reduce smoking relapse rates among individuals who are current CC smokers.

The withdrawal effects of CC's have been well characterized. Tobacco withdrawal has been generally defined as "a syndrome of behavioral, affective, cognitive, and physiological symptoms, typically transient, emerging upon cessation or reduction of tobacco use, and causing distress or impairment" (Shiffman, West, and Gilbert, 2004). Within 24-hours of abstinence from tobacco, individuals typically report increased levels of craving for tobacco, increase in negative affective states (e.g. feeling angry, impatient, anxious, or depressed) (Hughes, 2006; Piper et al., 2011), impaired cognition (Heishman, Taylor, and Henningfield, 1994; Shiffman, West, and Gilbert, 2004; Swan and Lessov-Schlaggar, 2007; Heishman et al., 2010), and decreased heart rate (Hughes, 1992). To date, there are only a small number of laboratory studies that have examined the ability of EC's to alleviate the aforementioned withdrawal symptoms. In a study by Bullen and colleagues (2010), following a 12-hour tobacco deprivation period, EC naïve CC smokers were allowed *ad libitum* access to a first-generation EC with 0 or 16 mg/ml nicotine concentration. Following using an EC with 0 or 16 mg/ml nicotine concentrations, participants reported reductions in negative affective states (i.e. irritability, restlessness, and difficulty concentrating) and cravings to smoke independent of nicotine concentrations, but to a lesser degree than following smoking a CC. In a study by Vansickel and colleagues (2010), EC naïve CC smokers who refrained from smoking for

12 hours administered 10-puffs from first-generation EC's that contained liquid with 16 or 18 mg/ml nicotine concentration, which significantly reduced cravings for smoking compared to baseline, though the reductions in cravings were less than those following smoking a CC. In another study by Vansickel and colleagues (2012), following a 12-hour tobacco deprivation period, EC naïve CC smokers administered six 10-puff bouts from a first-generation EC with 18 mg/ml nicotine concentration with 30-minutes between bouts, after which increases in heart rate and decreases in reported craving for smoking and negative affective states (e.g. anxiousness, restlessness, and irritability/frustration/anger) were reported. In a third study by Vansickel and Eissenberg (2013), regular EC users with minimal current CC use (< 5 cigarettes/day) administered 10-puffs from their own EC's (typically containing 18 mg/ml nicotine concentration) following a 12 hour EC and CC deprivation period. After administration of 10-puffs there were decreases in negative affective states (i.e. "anxious," "restlessness"), cravings for smoking and intentions to smoke, and an increase in heart rate relative to levels prior to EC use. In a study by Dawkins and colleagues (2012), following a 1-hour CC deprivation period, EC naïve CC smokers used a first-generation EC containing 0 or 16 mg/ml nicotine concentration *ad libitum* for a five-minute period. Following EC use, there were decreases in some negative affective states (contingent upon being male or female) in both 0 and 16 mg/ml nicotine concentration conditions vs. just holding an EC. Similarly, there were mixed effects on cognitive functioning with individuals in the 0 mg/ml condition making fewer errors on an attention task relative to individuals who just held an EC, and individuals in the 16 mg/ml condition making fewer recall errors on a memory task compared to individuals who just held an EC. In another study by Dawkins

and colleagues (2013), following 12-hours of tobacco deprivation, CC smokers used a second-generation EC containing 0 or 16 mg/ml nicotine concentration *ad-libitum* for 10 minutes. Compared to the 0 mg/ml condition, individuals performed better on a prospective memory task and reported greater reductions in negative affective state (i.e. anxiousness) and cravings to smoke after using an EC with 16 mg/ml nicotine concentration. In a study by Yan and D'Ruiz (2015), following 36-hours of tobacco deprivation regular CC smokers took 50-puffs from a first-generation EC containing 16 or 24 mg/ml nicotine concentration, followed by *ad-libitum* EC use for one hour. After taking 50-puffs and *ad-libitum* EC use, dose-related increases in heart rate were shown following EC use, with increases after using an EC with 24 mg/ml nicotine concentrations that were comparable to increases following smoking a CC. In a study by Lechner and colleagues (2015), following a 12-hour tobacco deprivation period regular CC smokers with minimal EC use were given five minutes of *ad-libitum* access to a first- or second-generation EC containing 16 mg/ml nicotine concentration. Following use, both first- and second-generation EC's reduced negative affective states and cravings to smoke, with greater reductions following second-generation EC's compared to first-generation EC's. Using a slightly different design than the previous studies, Norton and colleagues (2014) allowed a group of regular CC smokers to use a first-generation EC with 11 mg/ml nicotine concentration in lieu of a CC over a 72-hour period. After the 72-hour period, withdrawal symptoms were not significantly different than baseline levels. It is difficult, however, to interpret this finding because many individuals in this study did not successfully abstain from CC use during the 72-hour period, and there were

no other comparison conditions during the 72-hour period (e.g. abstinence from EC or CC use).

The aforementioned studies suggest that EC's can ameliorate some CC withdrawal symptoms, but typically to a lesser extent than CC's. Yet, there are several limitations to these studies that make interpreting their results difficult. One limitation is that all but one (Norton et al., 2014) of the previous studies did not collect pre-deprivation levels of the withdrawal symptoms and only collected measures immediately prior to using an EC. While previous characterizations of withdrawal can help to identify typical withdrawal symptoms, pre-deprivation measurements are required to validate the presence of a true withdrawal symptom. In recognition of this problem, Shiffman and colleagues (2004) suggest that stable baseline levels of candidate withdrawal symptoms be collected across multiple sessions, following unrestricted smoking, in order to obtain stable baseline levels of withdrawal symptoms. Then, pre-deprivation measurements can be used to determine true withdrawal symptoms as those that have changed relative to baseline levels following a deprivation period.

There is ambiguity in the literature as to when exactly tobacco withdrawal symptoms emerge. Most studies that have examined tobacco withdrawal symptoms have assessed post-smoking levels 24-hours or more since the beginning of tobacco deprivation (for review see Hughes, 2006). Thus, it is unclear when exactly withdrawal symptoms begin within 24-hours of tobacco deprivation. There is, however, evidence that some withdrawal symptoms (e.g. craving for smoking and heart rate) begin to manifest within 30 minutes following smoking (Hendricks et al., 2006). This might suggest that the ideal time to measure craving for smoking is immediately following the

last tobacco administration preceding a tobacco deprivation period. Yet, on other measures, acute smoking effects could confound measurements taken immediately after smoking. For example, there are well-characterized acute smoking effects on cognitive performance measures (Heishman, Kleykamp, and Singleton, 2010). Additionally, it has been shown that some self-report measures of tobacco withdrawal symptoms (e.g. difficulty concentrating, anxiety, sadness) do not begin to appear until at least 30-minutes following smoking (Hendricks et al., 2006). In recognition of the ambiguity of withdrawal symptom time course, measures in the current study were collected following *ad libitum* smoking conditions and immediately following smoking on baseline days. These data were used to help interpret the effects of smoking conditions on performance following tobacco deprivation.

Another limitation in the literature on alleviation of tobacco withdrawal symptoms by EC's is that none of the aforementioned studies examined different concentrations of nicotine within the same device, and selected only one nicotine concentration and compared it to an EC with 0 mg/ml. Thus, it remains uncertain whether there is a dose-dependent relationship between nicotine concentration in EC's and their ability to ameliorate tobacco withdrawal symptoms. A final limitation is that the aforementioned studies typically used short deprivation periods (e.g. 1-12 hours of deprivation from tobacco). Although some tobacco withdrawal symptoms may occur soon after smoking, some may take longer to develop (as discussed in Hughes, 1992). Therefore, a longer period of tobacco deprivation may be required to examine some withdrawal symptoms.

Abuse Liability of Electronic Cigarettes

Little is currently known about the abuse liability of EC's. Abuse liability can be defined as the ability of a substance to act as a reinforcer or to elicit pleasurable mood states (Jasinski, Johnson, and Henningfield, 1984). Ability of an EC to alleviate tobacco withdrawal symptoms would likely contribute to its reinforcing efficacy. That is, if EC's were able to effectively alleviate aversive withdrawal symptoms, it could be predicted that they would have some degree of abuse liability when used in the presence of CC withdrawal symptoms. As such, the findings discussed in the previous section would suggest that EC's might have some abuse liability among CC smokers who are experiencing withdrawal symptoms.

Another way of assessing reinforcing efficacy is to use a choice procedure between an EC and another known reinforcer. To date, only one study has used this method. Vansickel and colleagues (2013) compared EC's to money, among regular CC smokers following 12 hours of CC abstinence, and found an average crossover value (the point that participants would choose money over 10 puffs of EC or CC) of $1.06 for first-generation EC's with 16 mg/ml vs. $1.50 for CC's. This suggests that EC's might have some abuse liability, but relatively less than CC's. Another method of assessing abuse liability is to measure drug liking with subjective effects measures (e.g. visual analog scales or Likert scales). Although ratings of drug liking do not account for a variety of other factors that might influence abuse liability of a drug (e.g. societal views of using the drug, known health risks, availability), this is considered an important aspect to the abuse liability of a drug (discussed further in Jasinski and Henningfield, 1989). Although scant, there are a few studies that have assessed liking of EC's in controlled laboratory studies.

In two separate studies, increases in measures associated with liking (i.e. 'pleasant,' satisfying,' taste good') were observed following administration of participants' own EC compared to levels prior to EC use (Vansickel and Eissenberg, 2012, Vansickel, Weaver, and Eissenberg, 2013). In an earlier study by Vansickel and colleagues (2010) participants rated first generation EC's with 16 or 18 mg/ml nicotine concentration significantly lower than CC's on measures of liking (i.e. 'satisfying,' 'pleasant'), suggesting a lower abuse liability for EC's compared to CC's. In a study comparing first generation EC's with 0 or 16 mg/ml nicotine concentrations, EC's with 16 mg/ml were rated higher on measures of liking (i.e. 'pleasant to use') compared to EC's with 0 mg/ml (Bullen et al., 2010), suggesting that presence of nicotine in an EC contributes to their abuse liability. This is congruent with research demonstrating nicotine dose-dependent relationships in abuse liability of CC's (Henningfield, Miyasato, and Jasinski, 1985). In a study comparing first-generation EC's with 18 mg/ml nicotine concentrations among regular EC smokers, participants endorsed "satisfaction" following EC use (Dawkins and Corcoran, 2014). In a study examining EC use over 72-hours, first-generation EC's with 11 mg/ml nicotine concentrations were rated less 'satisfying' than CC's (Norton, June, and O'Connor, 2014). In a study comparing the effects of first- and second-generation EC's with 18 mg/ml nicotine concentrations among regular EC users, greater ratings of 'satisfying' were reported following second-generation EC's compared to first-generation EC's (Farsalinos et al., 2014). This suggests that the specific type of EC being used contributes to the abuse liability of EC's.

Although the aforementioned studies provide some evidence for the abuse liability of EC's, there are several limitations that must be acknowledged. It has been

suggested that in order to effectively assess abuse liability, the drug under consideration should be administered in at least two different dosages, with placebo and positive control conditions for comparison (Jasinski and Henningfield, 1989). Although the abuse liability of an EC may represent factors beyond nicotine (e.g. visual and tactile stimuli associated with handling and inhaling vapor from these devices), nicotine likely constitutes a major contributor to the abuse liability of EC's (evidenced by Bullen et al., 2010). If this is the case, the fact that none of the aforementioned studies utilized a meaningful range of nicotine dose concentrations is a limitation on the research of abuse liability of EC's thus far. Additionally, some of these studies did not utilize a placebo condition or some type of positive control condition (i.e. a CC), making quantification of abuse liability difficult. As such, further research on the effects of multiple doses of nicotine and their relative effects compared to placebo and control conditions may better characterize the abuse liability of EC's.

Public opinion is divided on whether EC's could serve as a useful smoking cessation tool for CC smokers, or whether they pose an additional risk to public health. This reflects the lack of consensus on the health effects (for review see Callahan-Lyon, 2014) and abuse liability (for review see Evans and Hoffman, 2014) of these devices. In order for current or future users of EC's and public health officials to make informed decisions about EC use in the future, further research is required on both these issues. In order to provide information on the abuse liability and ability of EC's to alleviate withdrawal symptoms engendered by CC deprivation in individuals with minimal EC experience, a research study that examines the physiological, subjective, and cognitive

effects of multiple nicotine concentrations of EC's, on CC smokers deprived of tobacco for 24 hours, was conducted.

CHAPTER TWO: METHODS

Participants

Eight healthy adults (2 females), between 22 and 47 years of age, were recruited with online advertisements and flyers placed in the local community. Individuals responding to advertisements completed a telephone interview or Internet-based questionnaire comprised of questions about general health status and tobacco and electronic cigarette use history. Sample size was chosen based on previous abuse liability studies with similar designs (e.g. Vansickel and Eissenberg, 2012; Henningfield, Miyasato, and Jasinski, 1985; Babalonis et al., 2013). Individuals who met study criteria over the phone or Internet were invited into the lab for a screening visit. Screening visits consisted of a battery of medical and psychological questionnaires including the Structured Clinical Interview for DSM-IV (SCID), one-year timeline follow-back for CC use, Fagerstrom test for nicotine dependence, a drug-use history questionnaire, and blood chemistry, liver function, and urinalysis tests. To be eligible to participate participants had to report smoking an average of 10 or more tobacco cigarettes per day for at least one-year, and not report being a regular electronic cigarette user (defined as daily use of an EC for the past seven-days). Individuals were excluded if they had a history of significant medical illness (e.g., cardiovascular disease, neurological or psychiatric disorder), were currently pregnant or breastfeeding, or had any other condition that would increase risk for study participation. Each participant's screening information was examined and approved by a study physician before beginning study procedures. A total of eight volunteers initiated the study and all eight completed. The University of Kentucky's Institutional Review Board approved all study procedures.

Design

The study consisted of an initial practice day and four two-day blocks each comprised of two sessions occurring over two consecutive days. All sessions typically occurred at the same time each day. Baseline sessions were incorporated to capture measurements of participants following typical tobacco use behaviors, while deprivation days were used to measure changes from baseline following 24-hour tobacco deprivation, and relative changes following use of an EC or CC. A placebo-controlled, randomized within-subjects design was used to examine the behavioral effects of nicotine concentrations distributed by an EC on deprivation days. Treatment conditions consisted of smoking a preferred (i.e., own) brand cigarette (not blinded) or puffing from an EC delivering vapor from liquid with nicotine concentrations of 0, 8, or 16 mg/ml under double-blind conditions.

Schedule

Practice Day

Previous research has suggested that in order to effectively acquire nicotine from an EC, naïve users must be sufficiently practiced with use of an EC (Vansickel and Eiseenberg, 2012). In order to assure sufficient practice with the EC, and familiarity with study procedures, following 24-hours of tobacco deprivation all study participants completed a six-session practice day. During each session participants took ten puffs from an EC delivering vapor from liquid with 16 mg/ml nicotine concentration using a paced puffing procedure, described below, for a total of 60 puffs over the entire practice day. There were 30-minutes between each session and assessments measures were completed before and after each puffing bout to familiarize participants with the

measures. These data were collected but not analyzed due to possible practice and carry-over effects from the last nicotine administration.

Baseline and Deprivation Days

Participants were instructed to abstain from solid food and caffeine four hours prior to each session. Participants were provided with a standard fat- and caffeine-free snack shortly after arrival. Sessions lasted approximately one hour. At the start of every session participants completed field sobriety, breath (Alcohol Sensor III, Intoximeters, Inc.; piCO Carbon Monoxide Monitor, Bedfont Scientific), and urine tests (cocaine, benzodiazepine, barbiturate, marijuana, amphetamine, and opiate drug use using OnTrak TestStik, Varian, Inc.; pregnancy using Clearview HCG II, Unipath, Ltd). During CC and EC use participants were cued by a laptop computer to take 10 two-second puffs, with 30-second inter-puff intervals. Both CC's and EC's were inhaled through a mouthpiece connected to a volumetric transducer in order to verify whether the participant was inhaling in accordance to the puffing procedure. Since the volumetric transducer was not calibrated for an EC, these data were collected but not analyzed. Use of the volumetric transducer, however, did not impede or restrict inhalation of the EC or CC in any way.

Baseline and deprivation days in two-day blocks occurred on consecutive days with at least 48 hours separating each two-day block. During each session, assessment measures were completed approximately 20-minutes after arrival (immediately preceding EC or CC use), and immediately after EC or CC use. On baseline days, following unrestricted smoking prior to arriving at the lab, a non-blinded CC of the participants preferred brand was administered using the paced puffing procedure. On deprivation

days, following 24-hours of tobacco and nicotine deprivation (as verified by CO levels ≤ 6 ppm or 10% of their CO level from the previous baseline day [whichever was higher]), participants completed cognitive tasks and self-report questionnaires before and after using a single CC of their preferred brand (baseline and deprivation days), or EC containing liquid with a nicotine concentration of 0, 8, or 16 mg/ml (deprivation days).

Assessments and Tasks

Minnesota Nicotine Withdrawal Scale (MNWS)(Hughes and Hatsukami, 1986; Hughes and Hatsukami, 2008): Thirteen items from the MNWS were used to examine effects of tobacco deprivation and alleviation from withdrawal symptoms after CC or EC use. Two questions associated with sleep (i.e. "insomnia, sleep problems, awakening at night" and "dreaming or nightmares") were not used. Participants rated the following items on an ordinal scale ranging from 0 ("none") to 4 ("severe"): "angry, irritable, frustrated," "anxious or nervous," depressed mood or sad," desire or craving to smoke," difficulty concentrating," "increased appetite, hungry or weight gain," "restless," "impatient," "constipated," "dizziness," "coughing," "nauseous," and "sore throat."

Questionnaire Smoking Urges-Brief (QSU-B)(Cox, Tiffany, and Christen, 2001): This brief 10-item questionnaire assesses desire to smoke and anticipated relief from negative affect by EC or CC use. Responses are submitted by using a 100-point sliding scale anchored on the left by "not at all" and on the right by "extremely." Previous research has indicated that this scale is sensitive to CC withdrawal effects (West and Ussher, 2009).

Visual Analog Scale – Smoking Effects (VAS-SE)(Blank, Sams, Weaver, and Eissenberg, 2008): the VAS-SE is comprised of ten items that have been shown to be

sensitive to the effects of nicotine. Participants were asked to rate their current feelings related to each item by placing a mark on a 100-unit line with the left endpoint of this continuum labeled "Not at all" and the right endpoint labeled "Extremely." Items on the VAS-SE included the following: "confused," "dizzy," "headache," "heart pounding," "light-headed," "nausea," "nervous," "salivation," "sweaty," and "weak."

Visual Analog Scale – Post Smoking (VAS-PS): Six items were used to assess the effects of using an EC or CC. Participants were asked to rate their current feelings related to each item by placing a mark on a 100-unit line with the left endpoint of this continuum labeled "Not at all" and the right endpoint labeled "Extremely." Items on the VAS-PS included the following: "stimulated," "like the effects," "want to smoke again," "enjoy the e-cigarette," "crave the e-cigarette," and "get pleasure from the e-cigarette?"

Digit-Symbol Substitution Task (DSST): Participants completed a two-minute computerized version of the DSST *(McLeod, Griffiths, Bigelow, and Yingling, 1982)*. In this revised task a digit-symbol code, consisting of geometric patterns associated with numbers 1-9, is constantly displayed at the top of the screen. The geometric patterns are comprised of 9 white and black boxes in 3x3 rows and columns that correspond to buttons on a 9-key keypad. In the center of the screen a random test digit 1-9 is displayed. Participants are asked to replicate the geometric pattern at the top of the screen associated with the test digit by pressing keys in a top-to-bottom order on a 9-key keypad. The test digit changes after the participant has pressed at least one key for each of the three rows. Participants are given visual feedback after each key press to indicate whether they pressed the correct or incorrect key. The DSST has been shown to be sensitive to nicotine deprivation (Pickworth et al., 1996). Two outcome measures from

this task were examined, total number of trials completed and percentage of trials completed that were correct.

Rapid Information Processing Task (RIP)(Fillmore, Marczinski, and Bowman, 2005): Participants completed a 5-min computerized version of the rapid information-processing task. During this task single digits were presented on-screen at a rate of 90 digits/min. Participants were instructed to press a key whenever three consecutive odd or even digits were presented. Initially, each digit was displayed on-screen for 67 ms with an ISI of 600 ms. Based on performance, the presentation rate increased (after correct responses) or decreased (after incorrect responses). Previous research has shown that RIP performance is sensitive to CC nicotine yield in regular tobacco smokers who have undergone smoking deprivation (Wesnes and Warburton, 1984). Four outcome measures from this task were examined: average digit rate, reaction time to correctly identified sequences (hits), percentage of sequences correctly identified (proportion correct), and number of responses when a sequence was not present (commission errors).

Cardiovascular Measures: Heart rate and blood pressure were recorded using an automated blood pressure monitor (Dinamap Pro 200, General Electric) before and after each EC or CC use. Measurements were taken while the participant was seated and took approximately 60-seconds. Diastolic and systolic blood pressure were consolidated into estimated mean arterial pressure (MAP) by using the following equation:

$$MAP = \frac{systolic + 2\ (diastolic)}{3}$$

Drug

The Blu® (Lorillard Technologies, Inc; Greensboro, NC) rechargeable EC was used for this study. This EC was chosen as a representative of first generation EC's because of its wide availability throughout the United States. The white and tan colored Blu® EC with "Classic Tobacco" liquid flavoring was used to best approximate a CC. Liquid tanks offered by the manufacturer with varying nicotine concentration (i.e. "none" 0 mg/ml, "low" 6-8 mg/ml, and "high" 14-16 mg/ml) were used to experimentally manipulate nicotine concentrations. Each disposable liquid tank was used for a maximum of four 10-puff sessions. Participants' preferred brand of CC was supplied for own brand (OB) conditions. Adherence to the paced puffing procedure was verified via video cameras and a volumetric transducer that tracked puffing behavior.

Data Analysis

To examine smoking on baseline days separate mixed models were fit for all variables, except VAS-PS variables, with session (pre-smoking on baseline days and post-smoking on baseline days) as the independent variable. To examine tobacco deprivation effects, two separate analyses were conducted. To examine the difference between unrestricted smoking and 24-hour tobacco deprivation separate mixed models were fit for all variables, except VAS-PS variables, with session (analysis 1: pre-smoking on baseline days and prior to EC or CC use on deprivation days; analysis 2: post-smoking on baseline days and prior to EC or CC use on deprivation days) as an independent variable. Differences between the aforementioned time points were evaluated for statistical significance by using t-tests to compare the least squares means derived by each mixed model. To examine acute EC or CC effects according to condition, a mixed

model was fit on withdrawal and acute effects measures with ratings following EC or CC use on deprivation days as the dependent variable, condition (own brand cigarette or EC with 0, 8 or 16 mg/ml of nicotine) as an independent variable, and ratings prior to EC or CC use on deprivation days as a covariate. When significant effects of condition were indicated, post-hoc pairwise comparisons of least-square means of each condition were conducted. To determine whether there were significant changes on withdrawal associated measures (i.e. RIP, DSST, MNWS, QSU-B, and HR and blood pressure) based on condition, a mixed model was fit on the difference between measures preceding and following EC or CC use on deprivation days with dose as the independent variable. When a significant effect of dose was indicated in these models t-tests were conducted for each condition to determine whether the difference between measures preceding or following EC or CC use was significantly different from 0. Hochberg's step-up procedure (Hochberg, 1988) was used to control error rates for each family of pairwise comparisons. Mixed models were fit using PROC MIXED in the SAS statistical software package, version 9.3 (SAS Institute Inc., Cary, NC). The alpha level for all analyses was set at 0.05.

CHAPTER THREE: RESULTS

Demographic and Clinical Variables:

Demographic and clinical variables are summarized in Table 3a. Participants were primarily Caucasian (87.5%) and male (75%), smoked an average of 19.7 ± 9.4 cigarettes per day, and had an average score of 5.6 on the FTND. Minimal alcohol use was reported, with all participants reporting some use at an average frequency of less than one day per week. Participants reported minimal marijuana use, with five non-users and three users reporting an average of 2.3 occasions per month.

Carbon monoxide levels decreased from an average of 29.0 ppm (SD=18.3) prior to smoking on baseline days, to an average of 5.5 ppm (SD=1.6) following 24 hours of tobacco deprivation. Average pre- and post-deprivation carbon monoxide levels for each participant are displayed in Table 3d.

Effects of OB smoking on baseline days (under column 'baseline smoking'), 24-hour tobacco deprivation (under column '24-Dep'), and measures following OB or EC use relative to measures prior to use (following 24-hr deprivation), are summarized in Table 3b. Direct comparisons between OB and EC use conditions are summarized in Table 3c.

RIP:

Baseline Smoking and Deprivation Effects: There were no significant changes in digit presentation rate, reaction time on correct trials, proportion correct, or commission errors after smoking OB on baseline days. Digit rate on the RIP significantly increased [$t(7)=4.76$, $p=.002$] from 90.7 digits per minute after smoking on baseline days to 98.8 digits per minute after 24-hours of tobacco deprivation; this rate was not significantly

different from pre-smoking rate on baseline days (Figure 3a). Reaction time on correct trials significantly decreased [i.e., improved, $t(7)=3.49$, $p=.01$] after tobacco deprivation from 346.5 ms after smoking on baseline days to 323.2 ms after 24-hours of tobacco deprivation; this time was not significantly different from the pre-smoking reaction time on baseline days. Proportion correct on the RIP significantly increased [$t(7)=4.15$, $p=.004$] from 55.8% correct after smoking on baseline days to 61.6% correct after 24-hours of tobacco deprivation; this rate was not significantly different from pre-smoking rate on baseline days.

Post-Deprivation OB or EC Effects: There were no significant changes in RIP task performance after OB or EC conditions.

DSST:

Baseline Smoking and Deprivation Effects: On baseline days, total trials completed during the two-minute DSST significantly increased [$t(7)=2.37$, $p=.05$] from 56.2 trials to 58.6 trials after smoking OB. After 24-hours of tobacco deprivation total trials completed significantly decreased [$t(7)=3.22$, $p=.01$] from 58.6 to 54.9 trials (Figure 3b), though 54.9 trials was not significantly different from trials completed pre-smoking on baseline days.

Post-Deprivation OB or EC Effects: A main effect of condition was observed on total trials completed [$F(3, 21)=3.18$, $p=.05$], with significantly more trials completed following using OB [$t(21)=2.85$, $p=.01$] and EC with nicotine levels of 8 mg/ml [$t(21)=3.11$, $p=.005$] compared to pre-smoking on deprivation days (Figure 3b). Based on the data presented in Figure 3b, which was counterintuitive to the statistical finding of significantly more trials completed following 8 mg/ml, a follow-up analysis of

performance measures prior to OB or EC use on deprivation days was conducted. This revealed a main effect of condition prior to OB or EC use [$F(3, 21)=7.56$, $p=.001$], with significantly fewer trials completed prior to 8 mg/ml compared to the 0 and 16 mg/ml conditions.

VAS-Smoking Effects:

Baseline Smoking and Deprivation Effects: On baseline days, ratings of 'dizzy' on the 100-point VAS scale significantly increased [$t(7)=2.41$, $p=.05$] from 0.3 to 4.0 after smoking OB. Ratings of 'heart pounding' significantly increased [$t(7)=3.05$, $p=.02$] from 0.3 to 4.3 after smoking OB and significantly decreased [$t(7)=2.93$, $p=.01$] from 4.3 to 0.5 following 24-hours of tobacco deprivation, though 0.5 was not significantly different from pre-smoking ratings on baseline days. On baseline days, ratings of 'lightheaded' significantly increased [$t(7)=3.62$, $p=.009$] from 0.2 to 6.0 after smoking OB and significantly decreased [$t(7)=3.59$, $p=.009$] from 6.0 to 0.2 after 24-hours of tobacco deprivation; 0.2 was not significantly different from pre-smoking ratings on baseline days.

Post-Deprivation OB or EC Effects: On deprivation days, a main effect of condition was observed on change in feeling 'lightheaded' after OB or EC use [$F(3, 21)=8.90$, $p<.001$], with significantly higher ratings following smoking OB [$t(21)=4.31$, $p<.001$] compared to pre-smoking. A relative difference between conditions was indicated on feeling 'lightheaded' [$F(3, 20)=7.49$, $p<.002$], with significantly higher ratings of feeling 'lightheaded' following OB (19.1) compared to EC nicotine levels of 0 (0.8), 8 (2.8), or 16 mg/ml (0.9).

MNWS:

Baseline Smoking and Deprivation Effects: On baseline days, ratings of 'desire or craving to smoke' on the five-point MNWS significantly decreased [$t(7)=6.94$, $p<.001$] from 1.8 to 0.5, ratings of 'dizziness' significantly increased [$t(7)=2.85$, $p=.03$] from 0 to 0.3 and ratings of 'sore throat' significantly increased [$t(7)=3.12$, $p=.02$] from 0 to 0.2 after smoking OB. Ratings on eight of the 13 MNWS items (i.e. feeling 'angry, irritable, or frustrated,' 'depressed mood or sad,' 'desire or craving to smoke,' 'difficulty concentrating,' 'increased appetite, hungry, or weight gain,' 'restless,' 'impatient') significantly increased from post-smoking on baseline days to after tobacco deprivation, with levels all exceeding those reported pre-smoking on baseline days. Ratings on three of the 14 MNWS items (i.e. feeling 'dizziness,' 'coughing,' 'sore throat') significantly decreased after tobacco deprivation, although they did not decrease below levels reported pre-smoking on baseline days. Total Scores on the MNWS ranged from 0-52 and significantly increased [$t(7)=5.48$, $p<.001$] from 2.3 to 7.2 after 24-hours of tobacco deprivation, which exceeded levels reported pre-smoking on baseline days.

Post-Deprivation OB or EC Effects: On deprivation days, a main effect of condition was observed on change in rating of 'desire or craving to smoke' [$F(3, 21)=3.29$, $p=.04$], with significantly lower ratings following smoking OB [$t(21)=5.34$, $p<.001$] compared to pre-smoking ratings. A relative difference between conditions was indicated on feeling 'desire or craving to smoke' [$F(3, 20)=5.17$, $p=.008$], with significantly lower ratings following OB (0.6) compared to EC nicotine levels of 0 (2.5), 8 (1.9), or 16 mg/ml (2.0). A main effect of condition was indicated on 'coughing' [$F(3,$

20)=3.11, p=.05], but there were no significant differences between conditions after correcting for multiple comparisons.

QSU-B:

Baseline Smoking and Deprivation Effects: On baseline days, ratings on nine of 10 items of the 100-point QSU-B scale decreased after smoking OB. The largest decreases were observed on 'if it were possible I would probably smoke now,' which decreased from 49.8 to 8.0 following smoking OB, and ''I am going to smoke as soon as possible,' which decreased from 44.9 to 8.6 following smoking OB. After 24-hours of tobacco deprivation, ratings on all variables of the QSU-B significantly increased. All of these increases, except those reported for 'smoking would make me less depressed,' significantly exceeded ratings reported prior to smoking on baseline days. The largest increases were observed on 'if it were possible I would probably smoke now,' which increased from 8.0 to 75.2 following 24-hours of tobacco deprivation, and 'I am going to smoke as soon as possible,' which increased from 8.6 to 69.8 following 24-hours of tobacco deprivation.

Post-Deprivation OB or EC Effects: A main effect of condition was observed on change in rating of 'I have a desire for a cigarette right now' [F(3, 21)=7.44, p=.001], with significantly lower ratings following smoking OB [t(21)=6.51, p<.001] compared to pre-smoking on deprivation days. Comparable main effects of condition were observed on all other QSU-B variables except 'nothing would be better than a cigarette right now,' 'I could control things better right now if I could smoke,' 'I would do almost anything for a cigarette now,' and 'smoking would make me less depressed,' which did not show significant changes following OB or EC use compared to levels prior to OB or EC use on

deprivation days. Between conditions, on 'I have a desire for a cigarette right now' there were significantly lower ratings following OB (18.4) compared to EC nicotine levels of 0 (58.4), 8 (50.4), or 16 mg/ml (56.4) (Figure 3f). Although following OB or EC use, no condition was significantly lower than levels prior to OB or EC use on deprivation days, between conditions, on 'nothing would be better than smoking a cigarette right now' there were significantly lower ratings following OB (12.5) compared to EC with 0 (40.5), 8 (36.8), or 16 mg/ml (39.9). Between conditions, on 'if it were possible I would probably smoke now' there were significantly lower ratings following OB (13.8) compared to EC nicotine levels of 0 (65.8), 8 (55.1), or 16 mg/ml (57.3). Between conditions, on 'all I want right now is a cigarette' there were significantly lower ratings following OB (15.9) compared to EC with nicotine levels of 0 (46.5) or 16 mg/ml (40.75). Between conditions, on 'I have an urge for a cigarette' there were significantly lower ratings following OB (13.5) compared to EC with 0 (59.4), 8 (50.5), or 16 mg/ml (46.1). Between conditions, on 'a cigarette would taste good right now' after OB or EC use [$F(3, 21)=4.87$, $p=.01$] there were significantly lower ratings following smoking OB [$t(21)=5.77$, $p<.001$] compared to pre-smoking on deprivation days. Between conditions, on 'a cigarette would taste good now' there were significantly lower ratings following OB (17.1) compared to EC with nicotine levels of 0 (55.5), 8 (46.1), or 16 mg/ml (51.0). Between conditions, on 'I am going to smoke as soon as possible' there were significantly lower ratings following smoking OB [$t(21)=5.00$, $p<.001$] compared to pre-smoking on deprivation days. Between conditions, on 'I am going to smoke as soon as possible' [$F(3, 20)=8.82$, $p=.006$] there were significantly lower ratings following OB (18.5) compared to EC with nicotine levels of 0 (64.6), 8 (52.5), or 16 mg/ml (57.5).

HR and MAP:

Baseline Smoking and Deprivation Effects: No significant changes in heart rate or mean arterial pressure were observed post OB smoking on baseline days. Heart rate significantly decreased [$t(7)=7.51$, $p<.001$] from 84.0 bpm to 72.5 bpm after 24-hours of tobacco deprivation, which was significantly lower [$t(7)=5.18$, $p=.001$] than pre-smoking on baseline days. Mean arterial pressure significantly decreased [$t(7)=4.35$, $p=.003$] from 102.6 to 96.0 after 24-hours of tobacco deprivation, though this level was not significantly lower than pre-smoking levels on baseline days.

Post-Deprivation OB or EC Effects: A main effect of condition was observed on heart rate [$F(3, 21)=3.45$, $p=.04$], with significantly higher heart rate following OB [$t(21)=4.95$, $p<.001$] compared to pre-smoking on deprivation days. A relative difference between conditions was indicated on heart rate [$F(3, 20)=8.82$, $p=.006$], with significantly greater heart rate following OB (90.1) compared to EC with nicotine levels of 16 mg/ml (75.0).

VAS-Post Smoking:

Post-Deprivation OB or EC Effects: A significant effect of condition was detected on ratings of 'stimulated' (Figure 3e) [$F(3, 21)=4.52$, $p=.01$] and 'enjoy the e-cigarette' [$F(3, 21)=4.34$, $p=.02$], with significantly higher ratings following OB compared to EC with 0 mg/ml. Significant effects of condition were also detected on ratings of 'like effects' [$F(3, 21)=5.23$, $p=.007$] and 'want to smoke again' [$F(3, 21)=11.82$, $p<.001$], with significantly higher ratings following OB (68.2) compared to EC with nicotine levels of 0 (26.8), 8 (29.4), or 16 mg/ml (38.4) (Figure 3d). A significant effect of condition was detected on ratings of 'get pleasure from the e-cigarette' [$F(3, 21)=4.34$,

p=.02], but there were no significant differences between conditions after correcting for multiple comparisons.

Table 3a. Demographic and Clinical Variables

	Total *N* = 8
Gender Female, *N (%)*	 2 (25.0)
Age, years (mean, SD)	34 ± 9.1
Education, years (mean, SD)	14.4 ± 2.1
Race Caucasian, *N* (%) Other, *N* (%)	 7 (87.5) 1 (12.5)
Fagerstrom Test for Nicotine Dependence Score, (mean, SD)	5.6 ± 2.1
Tobacco, cigarettes per day (mean, SD)	19.7 ± 9.4
Caffeine, days/week (mean, SD)	5.7 ± 2.6
Alcohol, days/week (mean, SD)	.82 ± .81
Marijuana, occasions/month (mean, SD)	.88 ± 1.6

Table 3b. **Cognitive, subjective, and physiological effects by session and condition**

Variable	Baseline Smoking	24-Dep	Baseline vs. 24-Dep	Own Brand	Electronic Cigarette Nicotine Concentrations		
					0 mg/ml	8 mg/ml	16 mg/ml
Rapid Information Processing Task							
Digit rate		↑**					
Reaction time on correct trials		↓*					
Proportion correct		↑**					
Commission errors							
Digit Symbol Substitution Task							
Total trials completed	↑*	↓*		↑**		↑**	
Percentage trials correct							
Visual Analog Scale – Smoking effects							
Confused							
Dizzy	↑*						
Headache							
Heart pounding	↑*	↓*					
Lightheaded	↑**	↓**		↑***			
Nausea							
Nervous							
Salivation							
Sweaty							
Weak							
Minnesota Nicotine Withdrawal Scale							
Angry, irritable, or frustrated		↑***	↑***				
Anxious or nervous							
Depressed mood or sad		↑*	↑*				
Desire or craving to smoke	↓***	↑***	↑***	↓***			
Difficulty concentrating		↑**	↑**				
Increased appetite, hungry, or weight gain		↑*	↑*				
Restless		↑*	↑*				
Impatient		↑**	↑**				
Constipated							
Dizziness	↑*	↓*					
Coughing		↓*					
Nauseous							
Sore throat	↑*	↓*					
Total Score		↑***	↑***				

Table 3b (continued).

Nothing would be better than smoking a cigarette right now	↓***	↑***	↑**				
If it were possible I would probably smoke now	↓***	↑***	↑***	↓***			
I could control things better right now if I could smoke	↓**	↑**	↑*				
All I want right now is a cigarette	↓***	↑***	↑**	↓***			
I have an urge for a cigarette	↓***	↑***	↑***	↓***			
A cigarette would taste good now	↓***	↑***	↑***	↓***			
I would do almost anything for a cigarette now	↓**	↑***	↑**				
Smoking would make me less depressed		↑*					
I am going to smoke as soon as possible	↓***	↑***	↑**	↓***			
Heart Rate and Blood Pressure							
Heart rate		↓***	↓**	↑***			
Mean arterial pressure		↓**					

Baseline smoking = results of comparisons between pre- and post-smoking on baseline days. 24-Dep = results of comparisons between post-smoking on baseline days and prior to OB or EC use on deprivation days. Baseline vs. 24-Dep = results of comparisons between pre-smoking on baseline days and prior to OB or EC use on deprivation days. Own brand and electronic cigarette nicotine concentration columns represent comparisons between condition and prior to OB or EC use on deprivation days. *$p \leq .05$, **$p \leq .01$, ***$p \leq .001$

Table 3c. **Cognitive, subjective, and physiological effects of using electronic cigarettes compared to own brand cigarettes**

Variable	Electronic Cigarette Nicotine Concentrations#		
	0 mg/ml	8 mg/ml	16 mg/ml
Rapid Information Processing Task			
Digit rate			
Reaction time on correct trials			
Proportion correct			
Commission errors			
Digit Symbol Substitution Task			
Total trials completed			
Percentage trials correct			
Visual Analog Scale – Smoking effects			
Confused			
Dizzy			
Headache			
Heart pounding			
Lightheaded	↓**	↓**	↓***
Nausea			
Nervous			
Salivation			
Sweaty			
Weak			
Visual Analog Scale – Post Smoking			
Stimulated	↓**		
Like effects	↓**	↓**	↓**
Want to smoke again	↑***	↑***	↑***
Enjoy the e-cigarette	↓**		
Crave the e-cigarette			
Get pleasure from the e-cigarette			
Minnesota Nicotine Withdrawal Scale			
Angry, irritable, or frustrated			
Anxious or nervous			
Depressed mood or sad			
Desire or craving to smoke	↑**	↑**	↑***
Difficulty concentrating			
Increased appetite, hungry, or weight gain			
Restless			
Impatient			
Constipated			
Dizziness			
Coughing			
Nauseous			
Sore throat			
Total Score			
Questionnaire of Smoking Urges – Brief			
I have a desire for a cigarette right now	↑***	↑***	↑***
Nothing would be better than smoking a cigarette right now	↑**	↑**	↑**
If it were possible I would probably smoke now	↑***	↑***	↑***
I could control things better right now if I could smoke			
All I want right now is a cigarette	↑**		↑**
I have an urge for a cigarette	↑***	↑***	↑***
A cigarette would taste good now	↑**	↑**	↑**
I would do almost anything for a cigarette now			
Smoking would make me less depressed			
I am going to smoke as soon as possible	↑**	↑**	↑**
Heart Rate and Blood Pressure			
Heart rate			↓**
Mean arterial pressure			

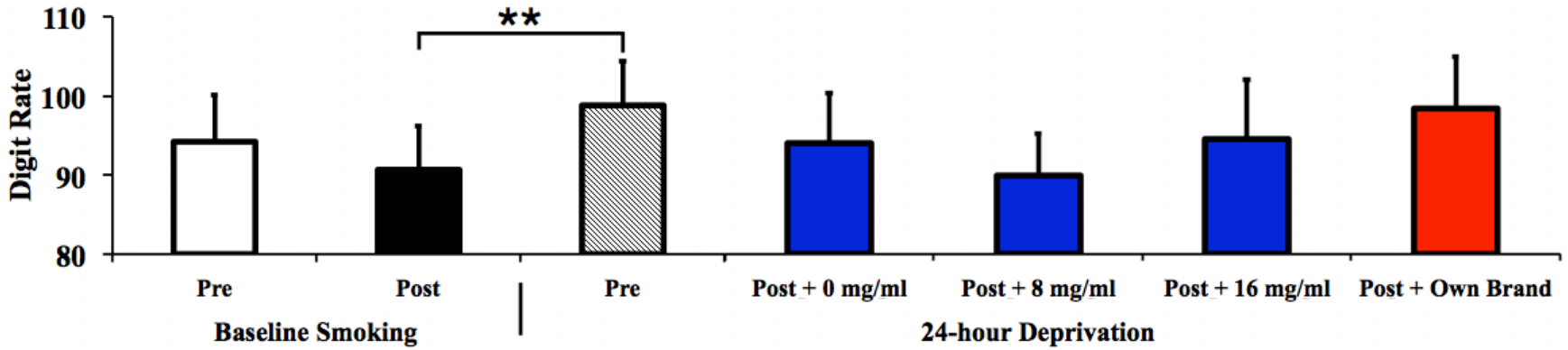
Table 3c. (continued)

#: Comparison with Own Brand smoking condition. Arrows represent values following EC use that were significantly above (🡅) or below (🡇) values for own brand cigarettes following EC use on deprivation days; **p*≤.05, ***p*≤.01, ****p*≤.001

Table 3d**. Carbon monoxide levels for each participant**

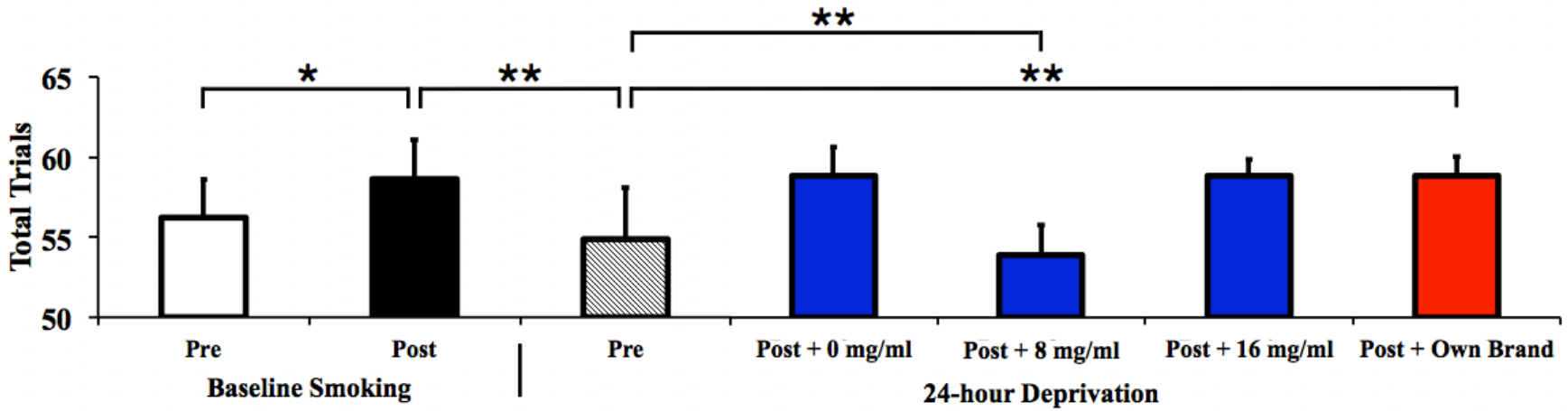
Participant #	Pre-smoking Baseline Days	Pre-smoking Deprivation Days
1	25.3	3.5
2	26.0	4.3
3	41.3	7.3
4	61.3	5.5
5	23.0	5.5
6	35.5	6.5
7	11.5	5.3
8	9.8	6.0
Total average	29.0 ± 18.3	5.5 ± 1.6

Figure 3a: Rapid Information Processing Task: Digit Rate



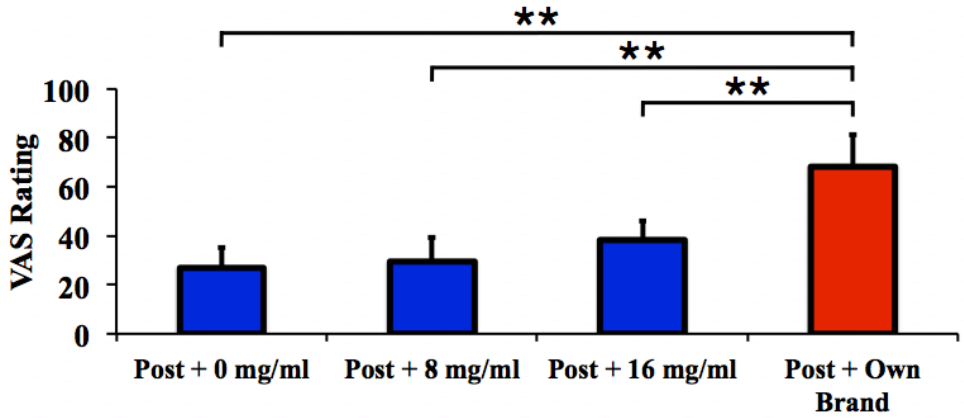
Average number of digits presented per minute on the Rapid Information Processing Task. After 24-hours of tobacco deprivation trial rate significantly increased [$t(7) = 4.76$, $p = .002$]. There were no statistically significant differences in trial rate following OB or EC use on baseline or deprivation days.

Figure 3b: Digit Symbol Substitution Task: Total Trials Completed Per Session



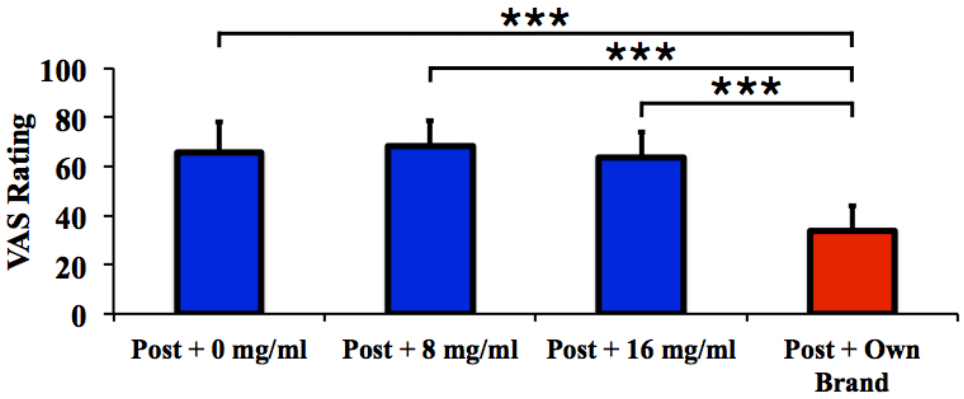
Number of trials completed on the two-minute Digit Symbol Substitution Task. A significant increase in total trials completed was observed following baseline smoking [$t(7) = 2.37$, $p = .05$] and a significant decrease was observed following 24-hour tobacco deprivation [$t(7) = 3.22$, $p = .01$]. Compared to levels prior to OB or EC use on deprivation days, there were significant increases in total trials completed following using electronic cigarettes dispensing vapor from the 8 mg/ml nicotine concentration [$t(21) = 3.11$, $p = .005$] or OB [$t(21) = 2.85$, $p = .01$].

Figure 3c: Self-report of "like effects"



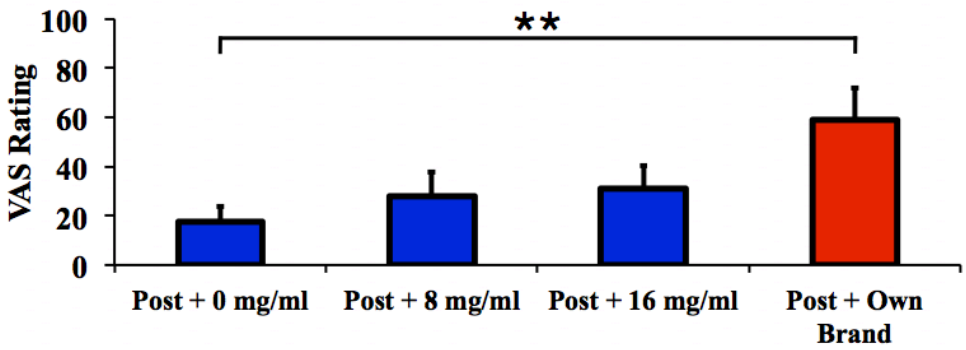
Self-report of "like effects" on a 100-point visual analog scale. Following OB or EC use after 24-hours of tobacco deprivation, own brand cigarettes engendered significantly greater reports of 'like effects' compared to electronic cigarettes with 0 [$t(21) = 3.56$, $p = .002$], 8 [$t(21) = 3.10$, $p = .005$], or 16 mg/ml [$t(21) = 2.89$, $p < .009$].

Figure 3d: Self-report of "want to smoke again?"



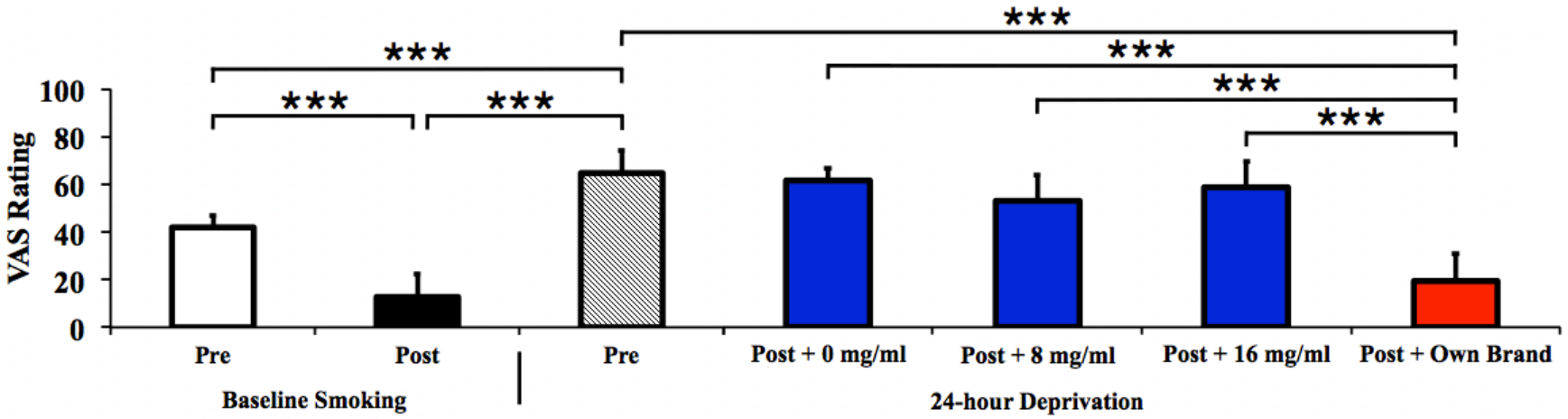
Subjective ratings of "want to smoke again?" on a 100-point visual analog scale. Following OB or EC use after 24-hours of tobacco deprivation, own brand cigarettes engendered significantly lower reports of 'want to smoke again' compared to electronic cigarettes with 0 [$t(21) = 5.55$, $p < .001$], 8 [$t(12) = 4.19$, $p < .001$], or 16 mg/ml [$t(12) = 4.39$, $p < .001$].

Figure 3e: Self-report of feeling “stimulated”



Subjective ratings of feeling “stimulated” on a 100-point visual analog scale. Following OB or EC use after 24-hours of tobacco deprivation, own brand cigarettes engendered significantly greater reports of ‘stimulated’ compared to electronic cigarettes dispensing 0 mg/ml nicotine [$t(21) = 3.50$, $p = .002$].

Figure 3f: Self report of "I have a desire for a cigarette right now"



Subjective ratings of "I have a desire for a cigarette right now" on a 100-point visual analog scale. A significant decrease was observed following baseline smoking [$t(7) = 7.45$, $p < .001$] and a significant increased was observed following 24-hour tobacco deprivation [$t(7) = 10.81$, $p < .001$]. Levels prior to OB or EC use on deprivation days were significantly higher than pre-smoking levels on baseline days [$t(7) = 5.71$, $p < .001$]. Following OB or EC use on deprivation days, own brand cigarettes engendered significantly lower ratings compared to electronic cigarettes dispensing vapor from 0 [$t(20) = 5.83$, $p < .001$], 8 [$t(20) = 4.73$, $p < .001$], or 16 mg/ml [$t(20) = 5.40$, $p < .001$] nicotine concentrations.

CHAPTER FOUR: DISCUSSION

Overall Conclusions

This study compared cognitive, self-reported, and physiological effects of a commercially available first-generation EC, with experimentally manipulated nicotine concentrations, to preferred brand CC's in a sample of regular tobacco smokers, following 24-hours of tobacco deprivation. Tobacco deprivation engendered typical self-report (MNWS and QSU-B) and physiological (heart rate) withdrawal symptoms. Smoking CC's after 24-hours of tobacco deprivation ameliorated many of the self-report (e.g. six of 10 QSU-B items) and physiological effects (heart rate) associated with tobacco deprivation. On all these measures of tobacco withdrawal, no attenuation of withdrawal effects from EC use was indicated. On key abuse liability measures (e.g., liking), there were no significant changes from ratings prior to EC use following EC use (regardless of nicotine concentration), while OB smoking engendered significant changes on these ratings.

Tobacco Withdrawal Symptoms

In order to assess tobacco withdrawal effects, participants were required to abstain from tobacco use for 24-hours prior to assessment of OB or EC use. Baseline data were collected prior to tobacco deprivation in order to determine relative changes following typical smoking behaviors (unrestricted smoking) compared to smoking after 24-hour tobacco abstinence. Self-reported symptoms of withdrawal (MNWS and QSU-B), exhaled CO levels, and heart rate all showed significant changes following 24-hour tobacco deprivation, which were commensurate with previous research on the effects of tobacco deprivation (e.g. Hughes and Hatsukami, 1986; Bell et al., 1999; Lee et al.,

2011). This verifies that the 24-hour deprivation period used in this study was effective at inducing tobacco withdrawal.

Withdrawal effects were defined as measures that significantly changed from levels following smoking on baseline days to levels significantly different from pre-smoking levels on baseline days after 24-hours of tobacco deprivation (e.g. heart rate). Acute effects were defined as measures that showed changes from pre- to post-smoking on baseline days and no significant deviation from pre-smoking levels on baseline days following 24-hours of tobacco deprivation. For example, lightheadedness increased from pre- to post-smoking levels on baseline days, while returning to levels not significantly different from pre-smoking levels on baseline days following 24-hours of tobacco deprivation. Similarly, total trials completed on the DSST increased following smoking on baseline days, while returning to levels that were not significantly different than pre-smoking levels on baseline days following 24-hours of smoking deprivations. On measures that followed this pattern, pre-smoking measurements on baseline days were compared to measurements after 24-hours of tobacco deprivation in order to determine if a withdrawal effect was present. In accordance with this criteria, dizziness (on the VAS-SE and MNWS), heart pounding, feeling lightheaded, sore throat, total trials completed on the DSST, and performance on the RIP were considered acute effects.

Following 24-hour tobacco deprivation digit rate increased on the RIP, which was likely driven by an increase in proportion correct (because commission errors did not significantly change following 24-hour tobacco deprivation), while reaction time on correct trials on the RIP decreased. There were no acute smoking effects on baseline days, which could suggest that changes in performance following 24-hour tobacco

deprivation on the RIP were due to tobacco withdrawal and not an acute effect. Yet, since performance on the RIP prior to OB or EC use on deprivation days did not significantly differ from performance prior to smoking on baseline days, it could not be concluded that changes in RIP performance were due to tobacco deprivation. There were also no significant changes in RIP performance following any the OB or EC conditions. This is incongruent with previous research reports showing changes in RIP performance following tobacco deprivation, and acute smoking of CC's (e.g. Wesnes and Warburton, 1984). This might be due to the large variance in performance on this task not attributable to OB or EC condition (evident in Figure 3a). Additionally, practice effects from multiple administrations of this task (before and after OB or EC use on baseline and deprivation days) may have confounded these results, such that clear effects of OB or EC use were not observable. Since the primary purpose of this study was to examine management of withdrawal symptoms by EC's compared to CC's, we cannot make any conclusions about the ability of EC's to manage cognitive withdrawal symptoms on this task due to a lack of a positive control.

Number of trials completed on the DSST significantly decreased following 24-hour tobacco deprivation but not relative to pre-smoking on baseline days. This suggests an acute smoking effect, which was replicated on deprivation days following smoking OB. Although there was a significant increase in total trials completed following 8 mg/ml EC's, Figure 3b demonstrates that performance following 8 mg/ml on deprivation days was actually decreased compared to other conditions. A follow-up analysis of performance on deprivation days, prior using OB or EC, indicated that total trials completed on days prior to using an EC with 8 mg/ml was significantly lower than

compared to total trials completed preceding all other conditions. Thus, this finding is likely a spurious result due to significantly lower performance on this measure prior to using an EC with 8 mg/ml days, and the lack of significant effects following 8 mg/ml on other measures employed in this study. These results suggest that smoking OB may enhance cognitive performance on the DSST regardless of deprivation, while using an EC does not. It has been suggested that changes in cognitive performance measured by laboratory tasks represents, in part, motivation for smoking, whereby use of tobacco could serve to enhance cognition (e.g., Evans and Drobes, 2009). Performance on total trials completed on the DSST in the current study support this notion. Since an acute effect of smoking OB was shown on the DSST, this might inform abuse liability rather than withdrawal management. Thus, these results would suggest that EC's have a lower abuse liability compared to CC's with regards to their effects on DSST performance.

Self-reported withdrawal effects were clearly indicated on several measures (i.e. seven items and total score on the MNWS, all QSU-B items). This is consistent with previous research using these measures in populations of regular tobacco users who have undergone a period of tobacco deprivation (Teneggi et al., 2002; West and Ussher, 2009; Lee et al., 2011). Following smoking OB, self-reported withdrawal symptoms on the QSU-B significantly decreased on baseline days (nine of 10 QSU-B items) and deprivation days (10 of 10 QSU-B items). Reports of 'desire or craving to smoke' on the MNWS and six QSU-B items measured on deprivation days significantly decreased following smoking OB and not using EC's, suggesting that EC's are less effective than OB at managing self-reported withdrawal symptoms. This evidence is consistent with previous studies that compared EC's to a CC in tobacco deprived regular CC smokers

and found that EC's were less effective than CC's at reducing tobacco withdrawal symptoms (Vansickel et al., 2010; Bullen et al., 2010; Norton, June, and O'Connor, 2014). Results of the current study, however, also found that EC's were unable to attenuate desires or cravings compared to pre-smoking levels, which is contrary to other studies that have shown some ability of EC's to attenuate cigarette cravings in regular CC smokers (Vansickel et al., 2010; Bullen et al., 2010; Vansickel, Weaver, and Eissenberg, 2012; Dawkins, Turner, and Crowe, 2013). There are multiple possible explanations for this. Relative to other studies, the current study used a longer period of tobacco deprivation, which may have yielded greater withdrawal effects that were more difficult to ameliorate with an EC. There is also a possibility that the specific device used in the current study might have been less effective at reducing cigarette cravings. For example, it has been demonstrated that EC's release differing amounts of nicotine into vapor, regardless of the concentration of nicotine in their liquid (Goniewicz, Hajek, McRobbie, 2014). Thus, it could be that the EC used in this study was not as capable at delivering nicotine to the user as were devices used in other studies.

Electronic Cigarettes and Abuse Liability

Measures of liking (i.e. VAS-PS) were sensitive to smoking OB on baseline and deprivation days. Participants rated OB significantly higher on 'like effects' compared to all nicotine concentrations of EC (Figure 3c), suggesting greater abuse liability for CC's compared to the EC conditions tested in this study. This is congruent with the only other studies that have compared EC's to CC's on some measure of liking (Vansickel et al., 2010; Norton, June, and O'Connor, 2014). Although to a lesser extent than CC's, participants did endorse some liking for the EC (average of 31.5 across all EC nicotine

concentrations), which was independent of nicotine concentrations. This suggests that EC's have some abuse liability independent of nicotine concentrations, although to a lesser extent than CC's. Based on the absence of nicotine-concentration-related effects, it could be argued that this is because the EC provides some of the cues associated with CC smoking (e.g. tactile and visual similarity of the device, and similar inhalation behavior compared to CC's), which are conditioned reinforcers due to a history of these stimuli being paired with nicotine delivered in CC's. If this were the case these, this might suggest that EC's would have a lower abuse liability amongst individuals who have never used CC's. Yet, since this is the only study thus far to examine multiple nicotine concentrations administered with the same device, further research should confirm these findings before any firm conclusions are drawn.

There were significant changes seen in heart rate following smoking OB, but not after smoking EC. This is commensurate with some previous research on EC's (Vansickel et al., 2010), yet inconsistent with other research (Vansickel, Weaver, and Eissenberg, 2012; Vansickel and Eissenberg, 2012). Inconsistencies among studies with regards to heart rate changes following using EC's might reflect variations in nicotine concentrations. Exemplifying this, Yan and D'Ruiz (2015) found that heart rate significantly increased following ad-lib use of a Blu® EC with 24 mg/ml nicotine concentration, while there was no significant change in heart rate following use of a Blu® EC with 16 mg/ml nicotine concentration. Furthermore, Yan and D'Ruiz (2015) found a positive correlation between plasma nicotine concentration and change in heart rate from before to after EC use. This corroborates prior research, which has shown increases in heart rate following administration of nicotine via multiple routes of administration (e.g.

Benowitz et al., 1982; Henningfield, Miyasato, and Jasinski, 1985; Parrott and Winder, 1989).

The lack of ability of EC's to alleviate withdrawal symptoms and reduced abuse liability compared to CC's in this study, in conjunction with the absence of heart rate effects following use of an EC, might suggest a lack of significant nicotine delivery. This would be congruent with a previous study that did not find significant elevations in plasma nicotine levels following 20-puffs from a first-generation EC with 16 or 18 mg/ml nicotine concentrations in a sample of EC naïve regular CC smokers (Vansickel et al., 2010). Vansickel and colleagues (2010) speculated that naivety to EC use might contribute to a lack of sufficient nicotine delivery. This speculation was supported by a follow-up study by this group that demonstrated effective nicotine delivery in EC naïve CC smokers following four 10-puff bouts from a first-generation EC with 16 mg/ml nicotine concentration (Vansickel, Weaver, and Eissenberg, 2012). Based on those findings, a comparable paced practice puffing procedure was incorporated into the design of the current study to increase the likelihood that participants would be sufficiently practiced to effectively use the EC. These procedures would be expected to enhance the functional efficacy of EC's relative to what would be encountered by smokers during initial exposure to EC's in the natural ecology. However, despite replicating the procedures demonstrated to be effective in the Vansickel et al (2012) study, the current study may not have been successful in training effective use of an EC, and insufficient levels of nicotine may have been delivered at even the highest nicotine concentration (16 mg/ml) tested. In light of this possibility, future research on EC's may want to incorporate procedures designed to verify nicotine delivery.

Limitations and Future Directions

There are several limitations to the current study that must be acknowledged. First, although the device used in this study was chosen based on its popularity and wide availability, results taken from this device may not generalize to other brands or types (e.g. second- or third-generation) of EC's. Second, this study examined EC's in individuals with minimal past EC experience. This was done in order to examine processes associated with initial use of an EC among regular CC smokers. Nonetheless, the effects reported in the current study may change as an individual gains more experience with an EC, as suggested by studies demonstrating that regular EC users are able to deliver behaviorally active nicotine doses (e.g. Yan and D'Ruiz, 2015). Third, a paced puffing procedure was used in order to increase the likelihood of functional use of the EC among study participants. Yet, it could be that more puffs are necessary to effectively deliver nicotine to the user (suggested by Vansickel, Weaver, and Eissenberg, 2012). Lastly, there may be individual differences that contribute to vulnerability to EC abuse liability, and by including subjects with prior but not current EC use individuals who were low in vulnerability to EC abuse may have been over-represented in this sample.

Conclusion

The current study demonstrated that, within the limitations of the nicotine concentrations that were tested and number of puffs administered, first-generation EC's have no measurable efficacy in ameliorating tobacco withdrawal symptoms in regular CC smokers and are definitely not as effective as tobacco cigarette smoking. Furthermore, measures of abuse liability suggest that while EC's may have some abuse liability under

conditions of tobacco deprivation among regular tobacco smokers, the magnitude of the liability is clearly lower than that of CC's.

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