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ABUSE LIABILITY OF AN ELECTRONIC CIGARETTE IN
TRADITIONAL CIGARETTE SMOKERS

A thesis submitted in partial fulfillment of the requirements for the degree of
Master of Science at Virginia Commonwealth University.

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B.S. Northern Kentucky University Spring, 2013

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List of Abbreviations

ANOVA	analysis of variance
CO	carbon monoxide
FTND	Fagerström Test for Nicotine Dependence
IRB	Institutional Review Board
min	minute(s)
mg	milligram
ng	nanogram (0.0000000001 grams)
NRT	nicotine replacement therapies
ml	milliliter
PG	propylene glycol
ppm	concentration in parts per million
VAS	visual analog scale
VG	vegetable glycerin

AbstractABUSE LIABILITY OF AN ELECTRONIC CIGARETTE IN
TRADITIONAL CIGARETTE SMOKERS

By Sarah F. Maloney, B.S.

A thesis submitted in partial fulfillment of the requirements for the degree of
Master of Science at Virginia Commonwealth University.

Virginia Commonwealth University, 2018

Major Director: Dr. Thomas Eissenberg, Department of Psychology and
Center for the Study of Tobacco Products

Thesis Chair: Dr. Alison Breland, Department of Psychology and
Center for the Study of Tobacco Products

Electronic cigarettes have grown in popularity across the U.S. and concerns have been raised about their abuse liability. The purpose of the current study was to evaluate and compare the abuse liability of an electronic cigarette with and without nicotine to a nicotine inhaler (the Nicotrol inhaler) and participants' own brand of cigarettes. A total of 24 smokers attended four sessions in which the abuse liability of each product was examined using the Multiple-Choice Procedure (MCP), nicotine delivery, nicotine abstinence symptom suppression, and subjective reinforcing effects. Results revealed that the nicotine containing and non-nicotine containing electronic cigarette had a higher reinforcing efficacy on the MCP than the nicotine inhaler, but on average had a lower reinforcing efficacy than participants own brand of cigarettes. The nicotine containing electronic cigarette delivered nicotine to participants in amounts that did not differ significantly from participants' own brand of cigarettes. The electronic cigarette with nicotine reduced nicotine abstinence symptoms to a greater degree than the electronic cigarette without nicotine, and both electronic cigarettes were rated as subjectively more reinforcing than

the inhaler but less reinforcing than participants' own brand of cigarettes. In sum, the results from this study suggest that the electronic cigarette examined had a moderate level of abuse liability that was higher than an FDA-approved nicotine inhaler but lower than traditional cigarettes. Furthermore, findings also suggest that electronic cigarette abuse liability may extend beyond factors related to nicotine delivery.

Abuse Liability of Electronic Cigarettes in Traditional Cigarette Smokers

Tobacco cigarette smoking is the leading cause of preventable death throughout the United States and the world (USDHHS, 2014). Cigarettes produce and expose users to over 7,000 compounds, many that are known carcinogens (USDHHS, 2014). Cigarettes cause numerous cancers and other diseases in smokers and nonsmokers that are exposed to tobacco smoke (USDHHS, 2014), and nearly 500,000 people die every year in the U.S. from smoking-related diseases (USDHHS, 2014). Cigarette use has been declining since 1965 due to various prevention efforts, but 15.5% of U.S. adults continue to smoke cigarettes (CDC, 2018), as these products are dependence-producing. Traditional cigarettes now share the market with a variety of novel tobacco products, including electronic cigarettes. Electronic cigarettes were released to the U.S. market in 2007 (Regan, Promoff, Dube, & Arrazola, 2013) and have been advertised as cigarette alternatives for smokers (Pearson, Richardson, Niaura, Vallone, & Abrams, 2012). Electronic cigarette use and awareness has increased dramatically in the past decade (Regan, Promoff, Dube, & Arrazola, 2013). These products have evolved substantially from early models, and newer models of electronic cigarettes are capable of delivering nicotine to some users in amounts similar to and exceeding that of traditional cigarettes (Lopez et al., 2016a; Wagener et al., 2017). The growing popularity of electronic cigarettes and the product's ability to deliver high amounts of nicotine to users has raised concerns amongst public health officials about electronic cigarette abuse potential, or the likelihood for these products to be used in excess and produce dependence. Therefore, the current study aims to investigate the abuse liability of an electronic cigarette in comparison to traditional cigarettes and the Nicotrol nicotine inhaler (a nicotine replacement therapy) in cigarette smokers. Determining the abuse liability of electronic cigarettes, relative to a product with a known high abuse liability (traditional cigarettes; Schuh,

Schuh, Henningfield, & Stitzer, 1997) and a product with a known low abuse liability (nicotine inhaler; West et al., 2000), will provide possible empirical evidence on the potential abuse of these products. Finally, the current study will help to inform policy decisions about the appropriate regulations needed for electronic cigarettes that are in accordance to products that are currently on the market with established low and high abuse liability.

Combustible Tobacco Cigarettes

Adult tobacco use. In the United States, cigarette smoking peaked in adults at 42.4% in 1965 (CDC, 1999) and through many prevention efforts has been reduced to 15.5% in 2016 (current every day or some days use; CDC, 2018). Men continue to have higher rates of smoking (17.5%) than women (13.5%; CDC, 2018). Although there are numerous tobacco products on the U.S. market, none are used with the frequency (somedays or daily) that traditional combustible cigarettes are used. For example, in 2015, only 4.3% adults used waterpipe/hookah, 2.5% of adults used oral or smokeless tobacco products, 1.8% of adults used cigars/cigarillos/little cigars, and 0.3% of adults used loose-leaf tobacco (CDC, 2016). The majority (87%) of adult cigarette smokers began smoking before the age of 18 and nearly all smokers (98%) began using cigarettes by age 26 (USDHHS, 2014). For this reason, some have referred to cigarette smoking as a pediatric disease (Kessler et al., 1997) and because of the early onset of smoking behavior, youth and adolescent rates of smoking are useful indicators of future adult smoking trends.

Adolescent tobacco use. Similar to adult smoking trends, adolescent cigarette use has also declined over the last four decades. In 1975, 36.7% of U.S. 12th grade students reported smoking at least one cigarette in the past 30 days (Johnston, O'Malley, & Bachman, 1999). Overall, use of cigarettes by high school students has decreased to 8.0% in 2016 (Jamal et al., 2017) and past 30-day cigarette use in 12th grade students has since decreased to 10.5% in 2016

(Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017). Cigarette use has also been reported among younger adolescent samples; recent data show that 4.9% of 10th grade students and 2.6% of 8th grade students reported smoking a cigarette in the past 30 days (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). While smoking rates have been declining, adolescent and adult tobacco use prevention remains a public health priority due to the detrimental effects that cigarette smoking and nicotine, the psychoactive chemical found in tobacco products, has on the body and the developing brain. (Corey et al., 2013; England, Bunnell, Pechacek, Tong, & McAfee, 2015; Kandel, Hu, Griesler, & Schaffran, 2007; Slotkin, 2002; USDHHS, 2014).

Health effects of tobacco use. In addition to nicotine, combusted cigarettes release over 7,000 compounds that have been found to cause numerous diseases (USDHHS, 2014). Cigarette smoke consists primarily of nitrogen, oxygen, and carbon dioxide (CO₂; e.g., Hecht, 1999). The smoke carries carcinogens such as polycyclic aromatic hydrocarbons (PAHs); *N*-nitrosamines, such as the nicotine-derived nitrosamine ketone (NNK), and arsenic into a user's lungs (e.g., Hecht, 1999). The International Agency for Research on Cancer has found 55 compounds in cigarette smoke that are carcinogenic in either humans or animals (Hecht, 1999). A more recent review described an additional 5 components of tobacco smoke to have carcinogenic risk and an additional 48 compounds have non-cancerous inhalation risks (Talhout et al., 2011). Chronic cigarette use can cause numerous cancers including those of the lung, kidney, liver, oropharynx, larynx, esophagus, trachea, bronchus, stomach, pancreas, ureter, cervix, and bladder, as well as acute myeloid leukemia and colorectal cancer. In addition to causing numerous forms of cancer, smoking can also cause a number of chronic diseases and conditions such as coronary heart disease, chronic obstructive pulmonary disease, asthma, congenital defects, stroke, blindness,

cataracts, pneumonia, diabetes, reduced fertility, hip fractures, and male sexual dysfunction (USDHHS, 2014). These diseases have also been found in adults and children who were exposed to chronic secondhand cigarette smoke (USDHHS, 2014). Nicotine has been found to have detrimental consequences on the developing brain in rodent models and in humans (Dwyer, McQuown, & Leslie, 2009). Clinically, these detrimental effects have been observed through higher incidence of SIDS, attention deficit hyperactivity disorder, substance abuse, and deficits in auditory-cognitive processing in children whose mothers smoked during pregnancy (Dwyer, McQuown, & Leslie, 2009). Furthermore, nicotine exposure in adolescents has been found to produce unique patterns of neural activation relative to that of adults has been found to increase vulnerability to addiction, mood disorders, and increased impulsivity (Dwyer, McQuown, & Leslie, 2009).

The morbidity and mortality associated with cigarette smoking comes at a high price. Medical care costs that are attributed to smoking-related illness and disease are estimated to exceed \$130 billion per year, and productivity loss from smoking-related illness is estimated to be over \$150 billion per year (USDHHS, 2014). Because of the serious health and financial consequences of cigarette smoking, preventing and reducing rates of smoking remains an important public health goal. In order to reduce the rates of cigarette smoking, researchers have studied a variety of factors that influence habitual cigarette use, as described below.

Reinforcing and dependence-producing properties of nicotine. The initiation of tobacco use is influenced by many factors, but sustained use is largely due to the dependence-producing drug nicotine (Henningfield, 2011; Henningfield & Keenan, 1993). Nicotine is a psychoactive chemical produced naturally by tobacco plants and is unique due to its ability to produce both stimulant effects and sedative effects, a phenomenon referred to as the “Nesbitt’s

paradox” (Nesbitt, 1973). Like other stimulants, acute nicotine exposure elevates blood pressure and heart rate (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Hughes & Hatsukami, 1986). The psychologically rewarding properties of nicotine are influenced by the amount (dose) of nicotine and the time it takes to reach the users’ brain; faster and higher doses of nicotine produce more rewarding effects in users (Benowitz, 1996). Nicotine can be absorbed into the blood-stream from the lungs, skin, gastrointestinal tract, buccal mucosa, and nasal mucosa (Meyer & Maurer, 2011). From the blood stream, nicotine binds to acetylcholine receptors in the central and the peripheral nervous systems. In the central nervous system, nicotine binds to ionotropic nicotinic receptors in the brain’s mesocorticolimbic, dopaminergic system (Govind, Vezina, & Green, 2009; Watkins, Koob, & Markou, 2000). When nicotine binds to these ionotropic nicotinic receptors it releases dopamine that produces psychological feelings of mild euphoria, increased energy, and heightened arousal (Benowitz, 1996; Pomerleau & Pomerleau, 1992; Stoleran & Jarvis, 1995). The rewarding effects from nicotine use increases the likelihood that an individual will repeat the behavior that produced the rewarding effects, also referred to as positive reinforcement. Chronic use of nicotine leads to neural network strengthening and upregulation of nicotinic acetylcholine receptors in the brain (Govind, Vezina, & Green, 2009). This change in brain structure and neural connectivity creates biological nicotine dependence in chronic users.

The aforementioned positive rewarding effects of nicotine are essential factors in establishing repeated tobacco use. In addition, chronic use of tobacco products is maintained largely by negative reinforcement (Eissenberg, 2004). Negative reinforcement occurs when an aversive outcome (e.g., nicotine withdrawal) is reduced by using the drug (e.g., tobacco product) increasing the likelihood that the behavior will be repeated. Nicotine abstinence syndrome (i.e.,

nicotine withdrawal) occurs when users discontinue the use of nicotine-containing products, which disrupts the neurological systems that were strengthened by the abundance of nicotine in these pathways. Somatic symptoms of nicotine abstinence syndrome are bradycardia (decreased heart rate), gastrointestinal discomfort, headache, increased appetite, and weight gain.

Psychological symptoms of nicotine abstinence syndrome include craving, depressed mood, irritability, anxiety, frustration, and difficulty concentrating (Cox, Tiffany, & Christen, 2001; Henningfield & Keenan, 1993; Shiffman, West, & Gilbert, 2004; Watkins, Koob, & Markou, 2000). These abstinence symptoms have been reported by cigarette smokers under a period of acute abstinence (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Drobles & Tiffany, 1997; Hughes, 2007; Hughes & Hatsukami, 1986) and under extended periods of abstinence (Gilbert et al., 1999). Some abstinence symptoms can occur hours after cigarette cessation and last for weeks, months, and sometimes years while the user's body adjusts to regain homeostasis. Somatic and psychological symptoms of abstinence syndrome can be almost immediately relieved by smoking a cigarette. These positive and negative reinforcing effects cause traditional cigarettes to be highly dependence-producing and make smoking cessation difficult.

Tobacco cessation. Nicotine dependence is generally believed to be the primary barrier to smoking cessation, although other factors have been found to influence cigarette dependence. As a result, therapies for nicotine/tobacco dependence have been developed to assist individuals in smoking cessation. These therapies fall into two categories: behavioral therapies and pharmacological therapies. Behavioral therapies include counseling, cognitive behavioral therapy, and social support, but have limited effectiveness. For example, six-month follow-up abstinence success rates for behavioral therapies have been reported in the range of 10.8% to 16.2% (Fiore et al., 2008). In addition to behavioral therapies, nicotine replacement therapies

(NRT) and non-nicotine-containing medications have been developed and approved by the Food and Drug Administration (FDA) to assist dependent cigarette users with smoking cessation. NRT help to alleviate some of the negative symptoms associated with abrupt cigarette cessation by replacing the nicotine that was once provided by cigarettes with alternative nicotine sources and then gradually tapering users off of nicotine. NRT comes in many forms: transdermal skin patches, gum, oral sprays, inhalers, and lozenges. Six-month quit rates have been found to vary across NRT, and are as follows: nasal spray (26.7%), high-dose nicotine patches (26.5%), long-term use of nicotine gum (26.1%), and nicotine inhaler (24.8%). Using a combination of NRT (e.g., patches plus gum) has been shown to be slightly more effective (Fiore et al., 2008). Although these products were changed from prescription to over-the-counter medications in 1996 to increase availability of these products to smokers, a population-based study found that it did not have any significant effect on the use of these products, the likelihood that a smoker made a quit attempt, the success of quit attempts, or population rates of smoking cessation (Thorndike, Biener, & Rigotti, 2002). Unfortunately, most smokers who use these products relapse (~74-90%) and continue smoking (Fiore et al., 2008).

Non-nicotine-containing medications (such as varenicline and bupropion) have been found to produce slightly better abstinence rates at six-month follow-ups. Varenicline (brand name Chantix) is a partial agonist and works by partially binding to nicotine receptors, which reduces craving (Potts & Garwood, 2007). Bupropion (brand name: Wellbutrin) is an antidepressant that has been found to improve some individuals' ability to abstain from smoking, although the factors contributing to this enhanced ability are not fully understood (Richmond & Zwar, 2003). Studies have shown that smokers using varenicline (2mg/day) had the highest rate of smoking cessation success (33.2%), followed by bupropion (24.2%). Even with the

availability of multiple treatments for smoking cessation, many smokers are still not successful and continue to smoke cigarettes. The high incidence of relapse has lead researchers to investigate other aspects of cigarette smoking that influence dependence in addition to nicotine.

Psycho-behavioral smoking-related stimuli such as hand-to-mouth gestures, the feeling of inhaling and exhaling smoke, and the sight and smell of smoke also play a role in cigarette dependence (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005). Interestingly, these psycho-behavioral smoking stimuli have been found to alleviate symptoms of nicotine abstinence without the presence of nicotine (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005), lending support to the psycho-behavioral theory of dependence. Thus, a product that provides these psycho-behavioral smoking cues and is also able to deliver nicotine to users could theoretically be an effective reduced harm or cessation aid product (Farsalinos et al., 2014). Currently, there are no FDA-approved cessation aid products that meets these criteria. However, a novel class of tobacco products, electronic cigarettes, were recently introduced to the U.S. market and have been used reportedly as smoking cessation aids by many cigarette smokers (Breland et al., 2017; Etter, 2010).

Electronic Cigarettes

The first electronic cigarette model was patented in China in 2003 (Patent No. 2518174 A1; Hon, 2003) originally, and was released into the U.S. market in 2007 (Breland et al., 2017; Regan, Promoff, Dube, & Arrazola, 2013). In less than a decade, these novel products have grown into a large class of devices that can be customized aesthetically and mechanically by the user (Evans & Hoffman, 2014). These products are similar in that they all contain a battery, a heating element, and a liquid reservoir. These products aerosolize a liquid that is contained in a reservoir (i.e., tank or cartridge) through a heating element (i.e., atomizer) that is powered by a battery.

Users inhale the aerosol through a mouthpiece, mimicking some of the psycho-behavioral smoking behaviors of traditional cigarettes. Electronic cigarette users can purchase electronic cigarette liquids in a variety of different nicotine concentrations and flavors (Zhu et al., 2014). The wide range of electronic cigarette liquid combinations and users' ability to customize newer models of electronic cigarettes makes it difficult to systematically evaluate these products and to generalize results across the product class. Correspondingly, as the electronic cigarette product class expanded, the awareness and curiosity about electronic cigarettes grew amongst adults and adolescents (Choi, Fabian, Mottey, Corbett, & Forester, 2012; Greenhill, Dawkins, Notley, Finn, & Turner, 2016; King, Alam, Promoff, Arrazola, & Dube, 2013). Alarming, electronic cigarette use has surpassed traditional cigarette use in adolescents, described in further detail below (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016).

Adult electronic cigarette use. In 2014, 12.6% of adults reported lifetime use of electronic cigarettes (Schoenborn & Gindi, 2015) and in 2016, 3.5% of adults were current electronic cigarette users (Phillips et al., 2017). Other studies have found prevalence rates of current electronic cigarette use to range from 6.5% to upwards of 31.0% in U.S. samples (Greenhill, Dawkins, Notley, Finn, & Turner, 2016). Higher rates of current electronic cigarette use were reported among younger adults ages 18-24 (5.2%), followed by adults ages 25-44 (4.3%), and older adults ages 45-64 (3.3%; Phillips et al., 2017). Current electronic cigarette use is more common among adults who are recent former cigarette smokers (one year or less; 22.0%) and current cigarette smokers (15.9%) than individuals with no smoking history (0.4%; Schoenborn & Gindi, 2015).

Adolescent electronic cigarette use. Lifetime use of electronic cigarettes has increased rapidly among U.S. adolescents (33.8% of 12th grade students) and has surpassed combustible

tobacco use (28.3% of 12th grade students; Greenhill, Dawkins, Notley, Finn, & Turner, 2016; Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016; Persoskie, Donaldson, & King, 2016). Data from the 2016 Monitoring the Future survey (an annual, national drug use surveillance survey) indicated that 12.5% of 12th grade students, 11.0% of 10th grade students, and 6.2% of 8th grade students reported using an electronic cigarette in the past-month (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). In 2016, rates of past 30-day electronic cigarette rates decreased slightly for high school students (8.0%) and middle school students (4.3%; Jamal et al., 2017). However, over 263,000 youth who had never smoked a cigarette used an electronic cigarette in 2013 (CDC, 2014). Furthermore, a study investigating adolescent curiosity about trying electronic cigarettes in never users found that 10.8% of students were “definitely curious” or “probably curious” about trying electronic cigarettes (Persoskie, Donaldson, & King, 2016). In addition, studies report that 28.5% to ~60% of adolescents use 0 mg/ml nicotine liquids, and 22.2% to 37.4% of adolescents use electronic cigarette liquid with nicotine (Miech, Johnston, O'Malley, Bachman, & Schulenberg, 2016; Morean, Kong, Cavallo, Camenga, & Krishnan-Sarin, 2016). Of great concern is that many (34.1%) of past-month adolescent electronic cigarette users did not know or were unaware of the nicotine concentration of their electronic cigarette liquid or device (Morean, Kong, Cavallo, Camenga, & Krishnan-Sarin, 2016). Therefore, some adolescents may be unaware that they are exposing themselves to nicotine. Nicotine exposure in adolescents is concerning because early exposure to nicotine can have damaging effects on the developing brain, as described earlier. Consequently, adolescents are more susceptible to nicotine dependence than adults (Doubeni, Reed, & DiFranza, 2010; England, Bunnell, Pechacek, Tong, & McAfee, 2015; Kandel Hu, Griesler, & Schaffran, 2007;

Slotkin, 2002; USDHHS, 2014). Thus, adolescent electronic cigarette use is an emerging public health concern.

Electronic cigarette device characteristics. Electronic cigarettes can be broadly categorized into two different models: “closed” systems and “open” systems. Closed system electronic cigarettes cannot be refilled or reused; instead, users buy replaceable liquid cartridges, or in some cases, entirely new electronic cigarettes. Disposable models of electronic cigarettes were the first devices to be introduced to the U.S. market, are aesthetically similar to cigarettes, and are sometimes referred to as “cig-a-likes” or “first-generation” models (Breland et al., 2017). In contrast, open system electronic cigarette devices vary greatly. Open models are reusable, refillable, and have replaceable parts and components (Breland et al., 2017). These systems range from user-friendly “pen” or “eGo” type devices to more advanced devices (e.g., “mechanical mods” or “mods”) that can be customized to users’ preferences. Many device modifications are intended to enhance the electronic cigarette (i.e., vaping) experience through the manipulation of device power. Battery voltage (V) and device resistance (R ; measured in Ohms) are the two determinants of device power (P ; measured in Watts). The manipulation of these variables, through modifications of the device battery, atomizer, and coil, gives users the ability to adjust the power of the device ($P=V^2/R$; Breland et al., 2017). Device power can influence device yield, and may influence nicotine delivery to the user (Shihadeh & Eissenberg, 2015; Soule, Lopez, Guy, & Cobb, 2016).

Electronic cigarette liquids. Electronic cigarette liquids are often called e-liquids or e-juices and typically consist of a mixture of solvents, flavorants, nicotine, and other additives (Wang et al., 2015). Propylene glycol (PG) and vegetable glycerin (VG) are common solvents in electronic cigarette liquids. To further customize the vaping experience, electronic cigarette

liquids are available in a range of PG/VG ratios. Propylene glycol has been classified as “Generally Recognized as Safe” (GRAS) by the FDA and is sometimes used in ointments, soaps, and salad dressings (Cobb, Byron, Abrams, & Shields, 2010). The long-term effects of propylene glycol inhalation are not yet known (Cobb, Byron, Abrams, & Shields, 2010). Further complicating matters, electronic cigarette liquids come in a range of flavors such as tobacco, menthol, fruit, candy, dessert, and beverage flavors (Bonhomme et al., 2016; Wang et al., 2015; Yingst, Veldheer, Hammett, Hrabovsky, & Foulds, 2017). Over 7,000 unique flavors of electronic cigarettes/electronic cigarette liquids have been documented (Zhu et al., 2014). The wide range of liquid flavors and flavor combinations makes determining the potential harm of repeated chemical flavorant inhalation difficult. Additionally, electronic cigarette liquid flavors enhance the rewarding properties of electronic cigarettes (Audrain-McGovern, Stasser, & Wileyto, 2016) and increase product appeal (Goldenson et al., 2016), described below in further detail.

Electronic cigarette nicotine delivery. Electronic cigarette liquids are also available in a variety of nicotine concentrations that often range from 0mg/ml to 36mg/ml (Breland et al., 2017). Owing to the variety of electronic liquids and devices, generalizations about nicotine delivery are difficult to make across the electronic cigarette product class (Cobb, Byron, Abrams, & Shields, 2010). Multiple studies have found that cig-a-like devices only deliver small amounts of nicotine to users (Farsalinos et al., 2014; Ramôa et al., 2016; Vansickel, Cobb, Weaver, & Eissenberg, 2010; Yan & D’Ruiz, 2015). More advanced electronic cigarette models have been found to deliver substantial amounts of nicotine to users (10.3 ng/mL; Farsalinos et al., 2014; Vansickel & Eissenberg, 2013), and some devices have been found to deliver nicotine to users in amounts comparable and sometimes exceeding that of traditional cigarettes (~15 ng/mL of

nicotine per 10-12 puffs; Ramôa et al., 2016; Wagener et al., 2017). Newer open system models of electronic cigarettes can be customized mechanically by users to increase power, which can increase nicotine yield, that is, the amount of nicotine emitted from the mouthpiece of the product (Farsalinos et al., 2014; Talih et al., 2015). In addition to power and liquid nicotine concentration, puffing behavior (puff topography) such as puff duration, can influence the nicotine yield of an electronic cigarette (i.e., larger and longer puffs yield higher nicotine; Talih et al., 2015).

Electronic cigarette toxicant exposure. In addition to nicotine, electronic cigarettes have been found to produce and deliver other potentially harmful constituents. These constituents have been found in electronic cigarette aerosols and are produced from the thermal breakdown of electronic cigarette liquid (Breland et al., 2017). These toxicants and carcinogens include: volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), metals, and formaldehyde (Costigan & Meredith, 2015; Tayyarah & Long, 2014; Tierney, Karpinski, Brown, Luo, & Pankow, 2016; Varlet, Farsalinos, Augsburger, Thomas, & Etter, 2015; Walley & Janssen, 2015). The data about electronic cigarette toxicant yield (the amount of toxicants emitted from the mouthpiece of the product) are mixed; some studies found toxicant yields (e.g., formaldehyde) of electronic cigarettes that were similar to what is found in tobacco smoke (Jensen, Luo, Pankow, Strongin, & Peyton, 2015; Kosmider et al., 2014). Other studies have found that compared with combustible cigarette smoke, electronic cigarette aerosols contain significantly fewer toxicants and have less pronounced effect on acute lung function (Flouris et al., 2013). Additional research will be needed to fully understand the gradient of toxicant exposure from various electronic cigarette devices and liquids, but the relatively unknown harms

about electronic cigarettes does not seem to have had an impact on individuals' perceptions of harm from these products, as described next.

Electronic cigarette perceptions and marketing. Electronic cigarettes have been advertised as reduced harm products and cessation aids (Pearson, Richardson, Niaura, Vallone, & Abrams, 2012), and such claims may have consequently shaped many individuals' perceptions about electronic cigarettes. Results from a variety of samples (i.e., young adults, electronic cigarette users, smokers) revealed that the majority (53% - 89%) of study participants perceive electronic cigarettes as less harmful and/or safer than combustible cigarettes (Adkison et al., 2013; Choi & Forester, 2013; Choi, Fabian, Mottey, Corbett, & Forster, 2012; Dockrell, Morison, Bauld, & McNeill, 2013; Etter & Bullen, 2011; Pearson, Richardson, Niaura, Vallone, & Abrams, 2012; Shi, Cummings, & Zhu, 2016). For example, 26.4% of a sample of 20-28 year olds who were aware of electronic cigarettes perceived them as being less addictive than tobacco (Choi & Forester, 2013). In addition, the majority of a sample of electronic cigarette users (82.9%) disagreed that second-hand aerosol is harmful to bystanders (Shi, Cummings, & Zhu, 2016). Finally, 28% of a sample of cigarette smokers perceived that electronic cigarettes were safer than nicotine replacement therapy (Dockrell, Morison, Bauld, & McNeill, 2013). These perceptions about electronic cigarettes are not limited to adults.

Adolescents also believe that electronic cigarettes are safer than combustible cigarettes. A study investigating adolescent perceptions of tobacco products revealed that adolescents perceived that electronic cigarettes had the least number of short-term and long-term health effects compared with traditional cigarettes, cigars, chewing tobacco, and hookah (Roditis, Delucchi, Cash, & Halpern-Felsher, 2016). These perceptions of reduced harm may account for a portion of the electronic cigarette users who reported using these products as a tobacco

alternative or cessation aid (Breland et al., 2017; Dockrell, Morison, Bauld, & McNeill, 2013; Etter, 2010).

Use of electronic cigarettes for smoking cessation. A common reason individuals report using electronic cigarettes is to aid in the reduction or cessation of cigarette smoking (Breland et al., 2017; Dockrell et al., 2013; Etter, 2010). Electronic cigarette enthusiasts report success stories of switching completely from traditional cigarettes to electronic cigarettes. In contrast, one cessation trial found that electronic cigarettes are no more effective than nicotine patches for short-term cigarette cessation (Bullen et al., 2013). More specifically, at the six-month follow-up, 7% of the participants randomized to the nicotine-containing electronic cigarette condition were abstinent, compared with the 6% in the nicotine patch condition, and 4% in the 0mg/ml nicotine electronic cigarette condition (Bullen et al., 2013). Additionally, other cessation studies have not found a significant relationship between electronic cigarette use and tobacco cigarette cessation (Breland et al., 2017; Kalkhoran & Glantz, 2016).

Abuse Liability

For any drug, drug abuse is defined as excessive non-medical drug use that is frequent and compulsive, and has become a significant feature in an individual's lifestyle (Jaffe & Jaffe, 1989). Abuse liability is the likelihood that a drug or a product will be used in excess and produce adverse consequences (Balster & Walsh, 2010; Jaffe & Jaffe, 1989). The likelihood for a drug or product to be abused is contingent on many factors such as the rate of drug delivery, sensory and subjective reinforcing effects, and social acceptability (see Figure 1; Balster & Walsh, 2010; Carter et al., 2009; Jaffe & Jaffe, 1989). The abuse liability of a drug or drug product is influenced by drug delivery, and specifically the pharmacokinetics and pharmacodynamics of the drug (Carter et al., 2009). Pharmacokinetics refers to the absorption,

distribution, metabolism, and excretion of the drug; the total dose and rate that a drug reaches a user plays an essential role in abuse liability (Benowitz, 1996). Drug platforms differ in their rate of delivery and their abuse potential. Additionally, products that deliver the same drug but through different routes/platforms can result in differing abuse liability. For example, delivery methods like intravenous injections and inhalation deliver drugs quickly to the users' brain and thus have a high abuse liability. Drugs that are used through these routes of administration (e.g., heroin, methamphetamine, and tobacco cigarettes) are abused often. In contrast, delivery methods like buccal absorption (i.e., mouth) and dermal absorption (i.e., skin) platforms have slower rates of drug delivery (Benowitz, Zevin, & Jacob, 1997) and, therefore, have lower abuse liability (e.g., nicotine patch; Carter et al., 2009; Schuh, Schuh, Henningfield, & Stitzer, 1997; West et al., 2000).

The pharmacokinetics of a drug has a direct influence on the pharmacodynamics of a drug. Pharmacodynamics refers to the physiological effects (i.e., increased heart rate, binding to brain receptors, etc.) and subjective effects (i.e., euphoric feelings) that a drug produces. As the rate and dose of drug delivery increases, the rewarding effects (i.e., euphoric feelings) and the likelihood for that drug or drug product to be abused also increases (Jaffe & Jaffe, 1989; Benowitz, 1996). For example, traditional cigarettes deliver nicotine quickly to users causing strong physiological and subjective rewarding effects (Henningfield & Keenan, 1993; Benowitz, 1996). Furthermore, NRT is not rated by smokers to be as satisfying or pleasant as cigarettes, largely owing to their slow and limited nicotine delivery (Schuh, Schuh, Henningfield, & Stitzer, 1997). In addition to the speed of nicotine delivery and magnitude of the pleasurable subjective effects produced by nicotine, the sensory experience (e.g., sight) of smoking can influence how pleasant or reinforcing a drug is to the user.

Sensory effects involved in smoking and electronic cigarette use behaviors include the sight, smell, taste, and feel of smoking/electronic cigarette use (Carter et al., 2009). Sensory effects like flavor can influence initiation of products and can have greater impacts among vulnerable subpopulations of individuals, such as youth (Carpenter, Wayne, Pauly, Koh, & Connolly, 2005). Following curiosity, flavors was the next most reported reason for trying electronic cigarettes among a sample of 340 adolescents (Bold, Kong, Cavallo, Camenga, & Krishnan-Sarin, 2016). Tobacco companies have used flavor additives in cigarettes to expand their consumer populations to novice and young smokers (Carpenter, Wayne, Pauly, Koh, & Connolly, 2005). Of all the different flavors that tobacco companies added to cigarettes, menthol was the most successful flavor additive. Subsequently, many menthol smokers report using menthol because it makes the overall sensory experience more pleasurable; specifically, smokers report that menthol cigarettes are less harsh and smoother than regular tobacco-flavored cigarettes (Ahijevych & Garrett, 2004). Since 2009, all flavor additives, except menthol, have been banned in cigarettes by the FDA (81 FR 28973, 2016), but this ban on flavor additives does not currently include electronic cigarette liquids. Flavored electronic cigarette liquids have been found to increase the pleasurable sensory effects of using an electronic cigarette (Audrain-McGovern, Stasser, & Wileyto, 2016), and not surprisingly, a national Population Assessment of Tobacco and Health (PATH) study that assessed flavored tobacco use found that 81% of the youth who tried an electronic cigarette, first tried a flavored electronic cigarette (Ambrose et al., 2015). Flavors activate multiple sensory systems (e.g., taste and smell) and therefore influence the product appeal and the likelihood of initiation.

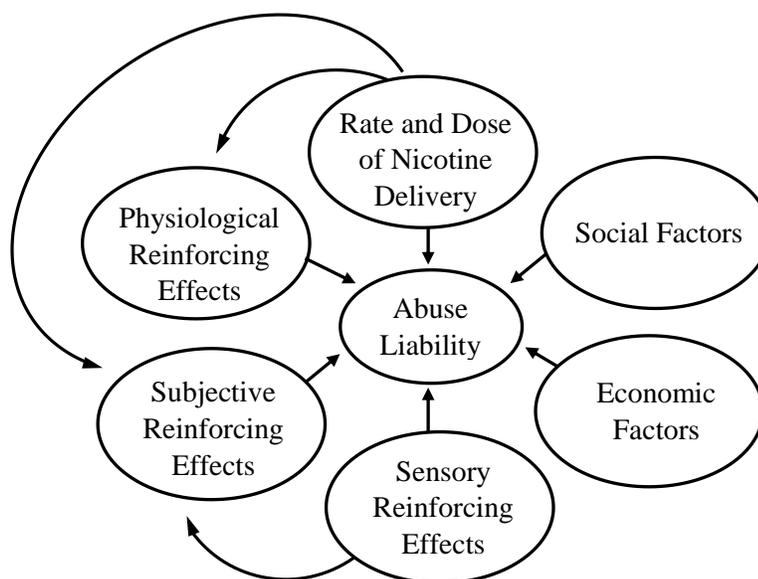


Figure 1. A conceptualization of various factors that impact abuse liability, with possible interactions between factors.

Abuse liability assessments. Abuse liability can be evaluated using a variety of methods, such as drug discrimination, acute dose-effect comparisons, assessment of subjective effects (i.e., craving suppression and drug liking), behavioral economic models, and choice procedures (Carter et al., 2009; Fischman & Foltin, 1991). Product appeal has also been considered a factor in abuse liability. Product appeal includes factors such as: contextual factors (e.g., taste, smell, feel, etc.); economic and environmental factors (e.g., cost and ease of obtainment); and social factors (e.g., marketing, risk/benefit claims, social acceptance, bans and regulations, beliefs and expectations; Carter et al., 2009; Henningfield, Hatsukami, Zeller, & Peters, 2011). These factors also influence the abuse liability of a drug or drug product (see Figure 1). Current electronic cigarette abuse liability research is limited, but several studies have been conducted that measured subjective effects, three studies examined self-reported electronic cigarette dependence, three studies used behavioral economic models to assess abuse liability, and two

clinical laboratory studies were conducted using choice procedures to examine abuse liability of electronic cigarettes. These studies are discussed in further detail below.

Subjective effects. The subjective assessment of rewarding effects and the subjective suppression of withdrawal and craving are important factors in the abuse liability assessments. As mentioned earlier, products that produce rewarding effects (i.e., rapid nicotine delivery or pleasurable sensory stimuli) have an increased likelihood of being used. For example, a study investigating subjective appeal of sweet flavored, non-sweet flavored, and flavorless electronic cigarettes measured subjective ratings of how much participants liked the electronic cigarettes, how likely they were to use it again, how much they would be willing to pay for a day's worth of use, perceived sweetness, and perceived throat hit. Participants (N = 20) attended one lab session and sampled ten flavors (peach, watermelon, blackberry, cotton candy, cola, sweet lemon tea, mint, tobacco, menthol, and flavorless) of electronic cigarettes at two nicotine concentrations (6mg or 0mg). Results indicated that nicotine did not have a significant effect on electronic cigarette appeal, although it was found to provide a stronger throat hit. However, participants indicated that they liked sweet flavored electronic cigarettes and were more willing to use sweet flavored electronic cigarettes compared with unsweet and flavorless electronic cigarettes. Thus, sweet flavored electronic cigarettes had greater subjective appeal than non-flavored electronic cigarettes (Goldenson et al., 2016). This study of subjective effects may indicate that flavor in electronic cigarettes could increase their likelihood for use and abuse potential.

Additionally, electronic cigarette devices and products that are capable of suppressing nicotine abstinence symptoms in nicotine-dependent smokers could result in a higher device/product uptake in smokers. Results from studies examining nicotine delivery and abstinence symptom suppression of electronic cigarettes have shown that electronic cigarettes

can suppress subjective nicotine abstinence symptoms in both smokers and current electronic cigarette users (Dawkins & Corcoran, 2014; Vansickel, Cobb, Weaver & Eissenberg, 2010; Vansickel & Eissenberg, 2013). A clinical abuse liability study examined the abstinence symptom suppression of a nicotine-containing electronic cigarette in comparison with participants' own brand of cigarettes. Results from this study revealed that an electronic cigarette filled with 18mg/ml nicotine concentration liquid was able to significantly reduce smokers' subjective feelings of nicotine abstinence following one 10-puff sampling bout and remained significantly lower after an additional five sampling bouts (Vansickel, Weaver, & Eissenberg, 2012).

Self-reported electronic cigarette dependence. In another study, researchers investigated electronic cigarette dependence in 111 electronic cigarette users that had switched completely from using traditional cigarettes (\geq one month abstinent) to electronic cigarettes. Current electronic cigarette dependence was assessed using a modified version of the first question of the Fagerström Test for Nicotine Dependence (FTND), which has also been referred to as the Fagerström Test for Cigarette Dependence due to its focus primarily being on cigarette dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) and a self-report rating of their current dependence on electronic cigarettes on a 100-point visual analogue scale (from 0 “not dependent” to 100 “extremely dependent”). Past cigarette dependence was also assessed using the first question on FTND and a self-report question in which participants were asked to rate their past dependence on traditional cigarettes on a 100-point visual analogue scale. Comparisons between past cigarette dependence and current electronic cigarette dependence revealed that participants were less dependent on electronic cigarettes compared with traditional cigarettes (Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013). Although this study

relies heavily on the accuracy of participant recall, it suggests that electronic cigarette use may not be associated with the high levels of dependence that is seen with traditional cigarettes, and therefore could be indicative of lower abuse liability. However, mixed results were reported in another dependence study of daily electronic cigarette users. In this study, participants completed measures of tobacco cigarette dependence that were modified to examine electronic cigarette dependence. A third (32.9%) of daily electronic cigarette users reported they would be successful at quitting electronic cigarette use, but another third of the sample (29%) reported that it would be very difficult or impossible to stop using electronic cigarettes (Etter & Eissenberg, 2015). This finding that a subset of electronic cigarette users would have difficulty quitting electronic cigarette use suggests that these products may have a higher abuse liability in some individuals than in others. In a study of 3,609 current electronic cigarette users, researchers compared participants' retrospective cigarette dependence to their current electronic cigarette dependence using the Penn State Cigarette Dependence Index and a modified version of the scale for assessing electronic cigarette dependence (Foulds et al., 2015). Participants reported that electronic cigarettes were less dependence-producing compared with traditional cigarettes. However, many electronic cigarette users in this study had strong cravings to use an electronic cigarette (35.4%) and a quarter (25.6%) reported feeling irritable when abstaining from electronic cigarette use (Foulds et al., 2015). Overall, these studies on self-reported current and retrospective dependence indicate that, in general, electronic cigarettes may be associated with lower abuse liability than traditional cigarettes, although a portion of electronic cigarette users may become dependent on these devices.

Behavioral economic methods. Several behavioral economic methods of assessing abuse liability have been used to examine electronic cigarettes. These methods have been based off of

traditional economic methods that have been used to examine the use patterns of electronic cigarettes. For example, researchers used quarterly sales data from a commercial store scanner database (from popular gas stations, drug stores, and groceries) to assess the cross-price demand elasticity (i.e., the responsiveness in the demand for one product as the price of another product changes) of electronic cigarettes and traditional cigarettes (Huang, Tauras, & Chaloupka, 2014). Using modeling, researchers incorporated several variables such as cigarette taxes, smoke-free policies, and cigarette price to estimate the price elasticity of the electronic cigarettes. The researchers found that a 10% increase in price would reduce sales of disposable electronic cigarettes by 12% and reusable electronic cigarettes by 19%. Furthermore, the models revealed that areas with higher cigarette prices would have higher electronic cigarette sales, although this was not statistically significant (Huang, Tauras, & Chaloupka, 2014). Although this study only had data from a limited segment of the electronic cigarette market (i.e., it did not include vape shop or online sales data), it demonstrated that increasing electronic cigarette prices would likely decrease electronic cigarette consumption among adults and youth.

Newer methods have been developed to examine the economics of purchasing behaviors, these methods are known as behavioral economic methods. For example, in a recent online study of an online Experimental Market Places (ETM), researchers had 840 smokers hypothetically shop with a balance credited based on weekly cigarette use expenses, at $\frac{1}{2}$ market price (MP), MP, 2x MP, and 4x MP in one control and in one of three ETM that had various products available: (1) conventional cigarettes, electronic cigarettes (disposable/cartridge/tank systems), and NRT (lozenges/patches/tablets) available; (2) conventional cigarettes, very low nicotine cigarettes, electronic cigarettes (disposable/cartridge/tank systems), and NRT (lozenges/patches/tablets) available; (3) conventional cigarettes, very low nicotine cigarettes, and

NRT (lozenges/patches/tablets) available; (4) very low nicotine cigarettes, electronic cigarettes (disposable/cartridge/tank systems), and NRT (lozenges/patches/tablets) available (Heckman et al., 2017). Results from ETM one revealed that as the price of conventional tobacco increased demand for conventional tobacco decreased, and the electronic cigarette cartridge, electronic cigarette tank, and NRT demand increased. Results from ETM two and three revealed that as price increased for traditional tobacco, demand for very low nicotine cigarettes and increased, and in ETM two demand for electronic cigarette cartridges increased. Results from ETM 4 revealed that when conventional forms of tobacco were unavailable, tank style electronic cigarettes were highest in demand, followed by very low nicotine cigarettes and cartridge electronic cigarettes. The results from this study suggest that increases in combustible cigarette prices could result in increased substitution of traditional cigarettes for electronic cigarette devices.

In addition to modeling electronic cigarette demand and price elasticity, behavioral economic purchase tasks try to mimic real-world demand by using hypothetical purchases of a given drug or product at increasing prices. The Cigarette Purchase Task (CPT; Jacob & Bickel, 1999) was developed and has been used to assess the demand curve of cigarettes and other tobacco products. In a study of 210 New Zealand smokers, the CPT was used to estimate the cross-price elasticity of electronic cigarettes and cigarettes (Grace, Kivell, & Laugesen, 2014). Participants rated how many electronic cigarettes and their own brand traditional cigarettes they would purchase at $\frac{1}{2}$ MP, MP, and 2x MP of their traditional cigarettes while the electronic cigarette price remained constant. Results revealed that participants would smoke on average 17.5 cigarettes per day if they were free and would stop purchasing cigarettes or “quit” if cigarettes cost NZ\$1.52 per cigarette. Overall, the demand for traditional cigarettes decreased as

price increased, and the demand for traditional cigarettes decreased by 35.8% when electronic cigarettes were available at ½ and regular market price. At 2x the market price, electronic cigarette availability did not decrease the demand for traditional cigarettes, instead 30% of participants reported they would quit smoking. However, 50% of the sample reported quitting traditional cigarettes at 2x the market price when electronic cigarettes were not available (Grace, Kivell, & Laugesen, 2014). This study used a hypothetical purchase task to examine the economic principles of supply and demand to predict changes in tobacco product consumption at differing prices and further examine how the prices of traditional cigarettes affect the uptake of electronic cigarettes. Results from this study yielded interesting results, in that at low and regular market prices electronic cigarette reduced the demand for traditional cigarettes, but at high market prices electronic cigarettes reduced the number of participants reporting that they would no longer purchase traditional cigarettes. This study illustrates the complexity of maximizing public health and minimizing public harm.

A more recent study used the CPT to examine the influence of flavor (tobacco vs. menthol; cherry vs. unflavored) and reduced harm messaging (reduced harm message or reduced carcinogen exposure message vs. no message) on electronic cigarette abuse liability, in comparison to participants' own brand cigarettes in a two-part experimental study (Barnes, Bono, Lester, Eissenberg, & Cobb, 2017). In this study participants were asked on the CPT how many times they would take 10 puffs from the electronic cigarette from each electronic cigarette condition (flavor/reduced harm message) at increasing prices. Results revealed that in both experiments participants would take on average 16.5, 10-puff bouts with traditional cigarettes and only about 7-11, 10-puff bouts from the various electronic cigarettes. In these experiments the quantity of puffs purchased as the price increased for puffs (i.e., demand elasticity), was

higher in the menthol condition with no harm message and the unflavored condition with a reduced harm message condition compared to the own brand cigarettes and the other electronic cigarette conditions indicating that these two conditions were more sensitive to price. Overall, the results from this study suggest that electronic cigarettes with and without flavors, and with and without reduced harm messaging, are less likely to be abused than traditional cigarettes, by traditional cigarette smokers. While this study was able to use the CPT to measure the abuse liability of electronic cigarettes via generalizing the instrument to a measurement of 10 puffs, other studies have investigated this issue further and has found that comparing electronic cigarette use to traditional cigarette use to be more challenging.

Comparing demand between electronic cigarettes and traditional cigarettes has posed measurement issues regarding quantifying use. For example, some researchers have asked if a single electronic cigarette use should be defined by a certain number of puffs, a time-frame of use, or certain amount of electronic cigarette liquid consumed. An electronic cigarette purchase task is currently being developed to address some of these measurement challenges (Cassidy, Tidey, Colby, Long, & Higgins, 2017). Researchers aimed to address how to accurately assess a single use of an electronic cigarette, and found it to be difficult because cigarette smoking episodes and electronic cigarette use episodes differed considerably between participants. Furthermore, there was considerable variability across participants' self-reported electronic cigarette use episodes in terms of the amount and the frequency of puffs taken from the electronic cigarette. Preliminary results from the study indicate that the breakpoint, or the price at which a participant would no longer buy puffs from an electronic cigarette, was on average at \$1.40 per puff; also, advanced electronic cigarette models had greater price sensitivity than closed system models. Overall, the current literature examining cross-price elasticity of

electronic cigarettes and traditional cigarettes suggests that electronic cigarette demand would increase as the price of traditional cigarettes increases and would also decrease as electronic cigarette prices increased.

Other behavioral economic methodologies have been used to assess the abuse liability of electronic cigarettes. An experimental auction examined the demand for electronic cigarettes by having participants bid on a reusable electronic cigarette starter pack, a single-use electronic cigarette, and a pack of Camel cigarettes in the participants' preferred flavor/type (menthol or tobacco; light or regular). The reusable starter kit had the highest average bid of \$10.31, followed by the single-use electronic cigarette that had an average bid of \$4.22, and the pack of cigarettes that had the lowest average bid of \$3.80 (O'Connor, Rousu, Bansal-Travers, Vogl, & Corrigan, 2016). This study highlights smokers' interest in electronic cigarettes and may suggest that individuals are willing to pay more for these products compared to traditional cigarettes. This study used a creative behavioral economic method to measure electronic cigarette demand; this study, in combination with the previous studies highlights the intricacy of measuring the abuse liability of electronic cigarettes.

Self-administration. Self-administration studies have been adopted from the animal literature into clinical studies and aim to assess the reinforcing effects of a drug by examining drug-taking behavior in comparison with another drug or placebo. A recent study using self-administration methods examined the impact of flavor on the rewarding and reinforcing value of electronic cigarettes in a sample of cigarette smokers. In this study, participants first sampled an unflavored, fruit-flavored, and a dessert-flavored electronic cigarette liquid that contained nicotine and chose one of the sweet flavors they liked best. Participants came back to the lab twelve hours abstinent from nicotine/tobacco and were given the option to earn puffs from the

electronic cigarette through earning points by clicking either a computer icon associated with the chosen sweet flavor liquid or a computer icon associated with the flavorless electronic cigarette liquid. Participants were willing to work almost six times harder (clicking targets in a computerized task) for puffs from a flavored electronic cigarette than for an unflavored electronic cigarette (Audrain-McGovern, Strasser, & Wileyto, 2016). This study suggests that electronic cigarette flavors increased the rewarding and reinforcing value of electronic cigarettes, and furthermore could indicate that sweet flavors may increase the likelihood that these products will be abused.

Choice procedures. Choice procedures have also been used to assess the abuse liability of electronic cigarettes, as well as other drugs and drug products. For example, the Multiple-Choice Procedure (MCP) involves having participants make discrete choices between a drug/drug product and increasing amounts of money. A choice (i.e., money or product use) is selected randomly and presented to the participant to keep or use. The MCP is a drug reinforcement procedure that was developed as a time-efficient, alternative technique to traditional drug discrimination procedures that can take up multiple days to obtain a single data point (Griffiths, Troisi, Silverman, & Miumford, 1993). The MCP is often chosen because of its forced choice reinforcement design and feasibility of implementation (Carter et al., 2009). Furthermore, the MCP has been validated with multiple drugs and drug platforms and has been able to detect dose-related effects, as well as drug avoidance (Correia & Little, 2006; Griffiths, Rush, & Puhala, 1996; Vansickel, Weaver, & Eissenberg, 2012). For this reason, the MCP is a useful tool to assess the abuse liability of nicotine and tobacco products because of its ability to compare new drug products with products that have established low abuse liability (e.g., NRT) and high abuse liability (e.g., traditional cigarettes; Carter et al., 2009). As a result, this method

of abuse liability assessment is ideal for examining novel tobacco products such as electronic cigarettes. To date, three clinical laboratory studies have used the MCP for this purpose. The first study had current smokers complete four sessions: first, they completed a sampling session in which they took six, 10-puff bouts from an 18mg/ml nicotine electronic cigarette in their preferred flavor (i.e., menthol or tobacco), and then they completed three experimental sessions. The three experimental sessions differed only by MCP product choices: participants' own brand cigarettes vs. electronic cigarette; money vs. electronic cigarette; and money vs. own brand cigarette. Participants valued their own brand of cigarettes higher (\$1.50) than the electronic cigarette (\$1.06) and a higher percentage of participants chose to receive own brand cigarette puffs over electronic cigarette puffs (Vansickel, Weaver, & Eissenberg, 2012). This clinical lab study suggests that the electronic cigarette tested has a lower abuse liability than traditional cigarettes.

A second study used the MCP to assess the abuse liability of a disposable electronic cigarette that contained about 24 mg/ml of nicotine compared to a traditional cigarette. A sample of 27 cigarette smokers completed four laboratory sessions. Participants first completed two separate sessions in which they had 15-minute unrestricted smoking or vaping sessions and then completed two separate sessions that differed by product (electronic cigarette or cigarette) in which they completed the MCP followed by one-hour product use/rest period. Finally, participants were asked if given the choice between a cigarette and an electronic cigarette, which they would choose. Results from this study revealed that cigarettes had a significantly higher crossover point (\$3.45) than the electronic cigarettes tested (\$2.73) and that given the opportunity to choose between smoking a cigarette or an electronic cigarette, 73.9% of participants preferred a cigarette to an electronic cigarette (McPherson et al., 2016).

The MCP has been used most recently been used with cigarette smokers to assess the influence of flavor (tobacco vs. menthol; cherry vs. unflavored) and reduced harm messaging (reduced harm message or reduced carcinogen exposure message vs. no message) on electronic cigarette abuse liability, in comparison to participants' own brand cigarettes (Barnes, Bono, Lester, Eissenberg, & Cobb, 2017). In this two-experiment study, abstinent smokers (N = 44) completed the MCP a total of five times and the CPT once (results discussed above). The average MCP crossover point was lower for all electronic cigarette conditions, except for tobacco flavored electronic cigarettes (\$1.38), regardless of the presence or absence of reduced harm messaging. Mean MCP crossover point was higher for cherry flavored (\$0.71) than for unflavored electronic cigarettes (\$0.51). In sum, these clinical studies suggest that electronic cigarettes have a lower abuse liability than traditional cigarettes in samples of cigarette smokers, and that flavor may influence electronic cigarette abuse liability. The potential for cigarette smokers to abuse electronic cigarettes may be lower than for traditional cigarettes and therefore could be a useful cigarette alternative product. Alternatively, these results could suggest low interest in use of these products and could indicate that electronic cigarettes are not viable reduced harm products for smokers, who have the most to benefit to gain from switching to electronic cigarettes.

In sum, a variety of abuse liability assessments are an important part of a comprehensive evaluation of electronic cigarettes. Understanding electronic cigarettes, rewarding subjective effects, their ability to suppress nicotine abstinence symptoms and product appeal will help inform public health officials of the probability that individuals will use this product as a tobacco alternative or for recreational purposes. Additionally, behavioral economic studies investigating the relationship between electronic cigarette prices and traditional cigarette prices will help state

and local regulators predict consumer behavior following product price increases or tax increases. Furthermore, self-administration studies suggested that sweet flavors increase the rewarding effects of electronic cigarettes and may have higher abuse liability than non-sweet flavors of electronic cigarettes. Finally, choice procedures indicate that nicotine-containing electronic cigarettes have a lower abuse liability than traditional cigarettes in cigarette smokers, which may provide support for exploring electronic cigarettes as potential harm reduction products for cigarette smokers

Regulatory Implications

The Food and Drug Administration (FDA) is entrusted with protecting the public health through ensuring that food, cosmetics, medical supplies, and prescription medications are safe and effective. The FDA gained authority to regulate tobacco products under the Family Smoking Prevention and Tobacco Control Act of 2009 (81 FR 28973, 2016). Tobacco products are difficult to regulate because of the extensive research demonstrating their harmful health effects. Therefore, the FDA uses different models to regulate these products. The FDA uses the public health standard to conduct risk/benefit evaluations among new and existing products and compare these risk/benefit evaluations between different subpopulations (e.g., smokers, youth, non-users, etc.). Cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco were the first products to be included in these FDA regulations, but in August, 2016 the FDA issued a rule which extended the definition of tobacco products to include electronic cigarettes, cigars, hookah tobacco, nicotine gels, and dissolvables (81 FR 28973, 2016). In order to develop policies and product regulations that best benefit the overall public health, the FDA requires an extensive amount of scientific data.

Systematically examining electronic cigarettes and understanding the potential benefits as well as the potential harm these products pose to public health, specifically vulnerable subpopulations, will help policy makers create appropriate product regulations. Thus, abuse liability studies play an important role and determining potential harm of electronic cigarettes as well as potential benefit for nicotine-dependent smokers. In addition, understanding the abuse liability of electronic cigarettes and examining the factors that are the most important in abuse liability such as nicotine delivery, nicotine abstinence symptom suppression, rewarding subjective effects, and product appeal, abuse liability studies could also help electronic cigarette manufactures develop products that fits within this harm/benefit model of the public health standard.

Statement of the Problem

Over the past decade, electronic cigarettes have evolved from simple devices that delivered very little, if any, nicotine to users, to devices that are capable of delivering high amounts nicotine and at speeds that mimic traditional cigarettes (Eissenberg, 2010, Wagener et al., 2017). The development of electronic cigarettes capable of delivering levels of nicotine that are similar to traditional cigarettes raises concern about their abuse liability. Subsequently, the electronic cigarette product class presents a unique problem for FDA regulation owing to the potential risks and benefits of these products. Traditional cigarette smokers have the most potential benefit from these products, as some electronic cigarettes have been found to produce fewer toxicants than traditional cigarettes (Flouris et al., 2013) and possibly reduce nicotine dependence in smokers (Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Vaudris, 2013). Although it is important to maximize the opportunity for smokers to access these products if they are true harm reduction products, it is essential to balance this benefit with the potential harm

from initiation of non-smokers and youth. There are only a few published clinical lab assessments of electronic cigarette abuse liability in cigarette smokers. Although these studies suggest that the abuse potential of electronic cigarettes is lower than that of traditional cigarettes (Farsalinos, Romagna, Tsiapras, Kyzopoulos, & Vaudris, 2013; McPherson et al., 2016; Vansickel, Weaver, & Eissenberg, 2012), there are there are no current studies examining the influence of electronic cigarette with and without nicotine on measures of abuse liability in comparison with NRT and with traditional cigarettes.

Purpose of the Present Study

The purpose of the current study was to systematically evaluate and compare the abuse liability of an electronic cigarette with and without nicotine to an FDA-approved NRT (the Nicotrol inhaler) and participants' own brand of cigarettes. In the current study, abuse liability was measured using the MCP (Griffiths, Troisi, Silverman, & Miumford, 1993), subjective effects ratings, and blood nicotine delivery.

Statement of Hypotheses

This study has four hypotheses: (1) based on previous literature that used the Multiple-Choice Procedure to evaluate the abuse liability of electronic cigarettes (Vansickel, Weaver, & Eissenberg, 2012), it is expected that participants will value their own brand of combustible cigarettes more than the electronic cigarettes, (2) participants will value the electronic cigarette with nicotine more than the electronic cigarette without nicotine, and the nicotine inhaler, (3) as suggested by previous research, combustible cigarettes and the electronic cigarette with nicotine will deliver more nicotine than the nicotine inhaler and the electronic cigarette without nicotine, and the combustible own brand cigarettes will deliver more nicotine than the electronic cigarette with nicotine (Breland et al., 2017; Ramôa et al., 2016; Vansickel, Cobb, Weaver, & Eissenberg,

2010), and (4) as suggested by previous research, nicotine abstinence symptoms, such as craving and irritability (as measured by multiple subjective measures), will be suppressed to a greater degree in the own brand cigarette condition and the electronic cigarette with nicotine condition, when compared with the nicotine inhaler condition and the electronic cigarette without nicotine condition (Vansickel, Cobb, Weaver, & Eissenberg, 2010).

Method

Participant Selection

A total of 24 traditional cigarette smoking volunteers completed this study. Sample size was determined by a priori power analyses using G* Power (Faul, Erdfelder, Lang, & Buchner, 2007) as well as effect size tables (Barcikowski, & Robey, 1985). These power analyses were conducted for the main outcome measures in the current study: the MCP crossover point, blood plasma nicotine levels, subjective effects of nicotine, and nicotine abstinence symptom suppression. For MCP crossover point, power analyses were conducted using the effect size from two previous studies that used the MCP; one had a large effect ($f = 0.77$; Vansickel, Weaver, & Eissenberg, 2012), and other had a small effect size ($f = 0.13$; McPherson et al., 2016). These power analyses results suggested that a sample size of nine to 34 participants would be sufficient to obtain ≥ 0.80 power to detect a true effect, assuming high (i.e., $r = 0.80$) correlations among repeated measures. Because of the discrepancy among effect sizes in the two studies, the mean effect size for both studies was used ($f = 0.45$) in further calculations, which suggested that a sample size of 20 participants would be sufficient to obtain ≥ 0.80 power to detect a true effect, assuming moderate (i.e., $r = 0.50$) correlation among repeated measures ($\alpha < .05$). Power analyses for blood plasma nicotine delivery were conducted similarly, using the effect size from a previous study that used similar laboratory methods ($f = .48$; Hiler, 2017); power analysis

results suggested that a sample size of eight to 18 participants would be sufficient to obtain ≥ 0.80 power to detect a true effect, assuming moderate (i.e., $r = 0.50$) correlation among repeated measures ($\alpha < .05$). Finally, power analyses were conducted with effect sizes from previous studies that examined the subjective effects of nicotine, specifically the item “Was the electronic cigarette satisfying?” ($f = 0.40$, Hiler et al., 2017; $f = 0.62$, McPherson et al., 2016) and nicotine abstinence symptom suppression, specifically the item “craving a cigarette/nicotine” ($f = 0.55$, Hiler et al., 2017); these analyses suggested that a sample size of five to 13 participants would be sufficient to obtain ≥ 0.80 power to detect a true effect, assuming moderate (i.e., $r = 0.50$) correlation among repeated measures ($\alpha < .05$). Lab studies generally have more control within them, including this within-subjects design and the conclusions for the all of all the power analyses suggested a small sample of five to 20 participants. Due to the range of suggested sample size, a total of 24 participants completed the study to ensure that six, 4-condition Latin squares can be completed and to ensure that the current study will be powered adequately to detect for all three main outcome measures if an effect truly exists.

Participants were recruited through word of mouth, local Craigslist advertisements, and Institutional Review Board (IRB) approved study fliers posted around local Richmond businesses. All experimental sessions took place at the Clinical Behavioral Pharmacology Laboratory (CBPL) located in Virginia Commonwealth University’s (VCU) medical campus. All participants were between the ages of 18 and 55 (mean = 30.92 years old, $SD = 9.5$), smoked ten or more cigarettes per day (mean = 16.33 cigs/per day, $SD = 6.6$) for at least a year (mean = 10.10 years, $SD = 9.1$), had an expired CO of 15ppm or more at screening (mean = 20.08 ppm, $SD = 5.0$ ppm), and were all willing to use an electronic cigarette in the lab. Individuals who self-reported any current health diseases or conditions, current psychiatric conditions, history of

chronic organ related disease, or high or low blood pressure, were not eligible to participate. Women who were currently pregnant (assessed by urinalysis) or reported breast feeding were not be eligible to participate. Individuals who self-reported regular use of prescription medications (excluding birth control or vitamins), past-month use of cocaine, opioids, benzodiazepines, methamphetamines, past 30-day use of marijuana >10 days, and past 30-day use of alcohol > 25 days were not eligible to participate. Participants' blood pressure and weight were measured and individuals with systolic blood pressure of 140 or greater, diastolic blood pressure of 90 or greater, or weighed under 110 pounds were not eligible to participate. Individuals who had used an electronic cigarette ≥ 20 times were considered to experienced electronic cigarette users and were not be eligible to participate in this study (Lee, Gawron, & Goniewicz, 2015). A total of 66 participants consented to participate in this study, 42 of those were found eligible, but 18 participants were discontinued due to following reasons: failure to follow-up (n = 6), lack of venous access (n = 3), failing to abstain (n = 2), high blood pressure (n = 2), scheduling conflicts (n = 1), enrolled in other ongoing studies (n = 1), undisclosed high blood pressure and prescription medication use (n = 1), needle phobia (n = 1), and difficulty understanding study tasks (n = 1). A final total of 24 participants completed this study.

Table 1.

Demographic Characteristics of the Sample (N=24).

Characteristic	Mean or N (SD or %)
Number Female	6 (25.0%)
Number NH Caucasian	6 (25.0%)
Number NH Black or African American	11 (45.8%)
Age (years)	30.9 (9.5)
Screen CO	20.1 (5.0)
Cigarettes/day	16.3 (6.6)
Duration cigarettes use (years)	10.1 (9.1)
Fagerström TND ^a	5.2 (2.0)
Penn State Dependence ^b	13.6 (4.5)
Number menthol smokers	17 (70.8%)
Education (years)	13.3 (2.2)
Unemployed	11 (45.8%)
Part or full time employed	10 (41.6%)

^a The Fagerström Test for Cigarette Dependence (Heatherton et al., 1986).

^b Penn State Electronic Cigarette Dependence Index (Foulds et al., 2014).

Screening and Informed Consent Procedures

All interested individuals from the community had to go through a two-part screening procedure. The first part of the screening procedure was conducted over the phone with CBPL study personnel or on the internet via the Center for the Study of Tobacco Products secure online registry. This first part of the screening process included a description of the study procedure and a short questionnaire of voluntary information concerning health status, tobacco use, electronic cigarette use, and alcohol and illicit drug use. Individuals who appeared eligible and who were interested in the study were scheduled to come into the CBPL for an in-person screening visit (the second part of the screening procedure). When individuals came in for the in-person screening visit they were seated in an individual session room and provided with a copy of the study consent form. A research assistant asked potential participants to follow along as they read the consent form out loud and answered any questions or concerns that arose during the explanation of the study procedure. After confirming full understanding of the study procedures, individuals had the opportunity to decide if they wanted to give consent to participate, decline to participate, or reschedule their screening visit if they needed more time to decide. After consenting to participate, participants were asked to complete several forms: the Health Information Questionnaire, the Fagerstorm Test for Nicotine Dependence (FTND) or previously known as the Fagerstorm Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), the Penn State Cigarette Dependence Index (Foulds et al., 2015), and a demographics questionnaire. Participants also had their vitals taken, an expired air CO breath test, and female participants were asked to provide a urine sample for a pregnancy test (Accutest Value hCG urine pregnancy test, Jant Pharmaceutical Corp). Eligible participants scheduled their sessions according to their preferences and availability. Reminder phone calls were made to each

participant one to two days before each scheduled session. During these calls, participants were reminded of the date and time of their session, as well as requirements for participation.

Procedures

Once screening was complete, eligible participants were scheduled for four separate lab sessions that were separated by a minimum of 48 hours and occurred no more than two times per week. In each session, participants used one of four study products: participants' own brand (OB) of cigarettes, an electronic cigarette with nicotine, an electronic cigarette without nicotine, and a nicotine inhaler. These four sessions were approximately five hours long, Latin-square ordered, and electronic cigarette conditions were double blind (keeping participants and staff blind to their own cigarette and the inhaler was not feasible). All sessions took place in VCU's CBPL, where participants completed sessions in separate session rooms, although multiple participants were sometimes in the laboratory at one time. Participants were required to come into the lab at least 12 hours abstinent from all nicotine and tobacco products and were asked to provide an expired air CO sample at the beginning of each session to verify abstinence from combustible tobacco (≤ 10 ppm, as in Lopez et al., 2016a). If participants did not meet this requirement, sessions were rescheduled and participants were reminded of study participation requirements.

Once a participants' expired air CO concentration was measured and recorded for study compliance, they were connected to physiological monitoring equipment that recorded heart rate and blood pressure continuously throughout the study session. After the baseline reading of blood pressure was taken, a nurse inserted an intravenous (IV) catheter into participants' forearm. Participants then completed baseline subjective questionnaires that assessed tobacco abstinence symptoms and other subjective symptoms (Hughes and Hatsukami Tobacco

Withdrawal Scale, Tiffany-Drobes Questionnaire of Smoking Urges—Brief, Direct Effects of Nicotine Scale, and the Direct Effects of Product Scale). Thirty minutes after IV insertion, the research nurse took a baseline 7 ml blood sample followed by subjective questionnaires. Then, participants sampled one of the study products during two, 10-puff use periods where participants were instructed to take 10 puffs with 30 second inter-puff-intervals. Participants then had 7 ml blood sample taken and completed the aforementioned questionnaires, with an additional questionnaire assessing the effects of the product (Direct Effects of Product Scale).

After sampling the product two times, participants had a 90-minute washout period. Following the 90-minute washout period, participants had a final blood sample taken, (in total, four blood samples were taken in each session), and then completed subjective questionnaires again. Immediately following the completion of the subjective questionnaires, participants' catheters were removed by the research nurse. After the research nurse had removed the catheter and answered any questions or concerns participants had, participants were asked to complete the Multiple-Choice Procedure, MCP (described in further detail below; Griffiths, Troisi, Silverman, & Miumford, 1993; Vansickel, Weaver, & Eissenberg, 2012). Immediately following the MCP, participants filled out the Hughes and Hatsukami Tobacco Withdrawal Scale. This procedure was repeated a total of three times with a rest period of 20 minutes in between MCP tasks. Participants could earn up to \$30.72 from the MCP, although this did not occur. After participants completed the last MCP task and subjective measures, physiological data collection equipment was disconnected and participants were thanked and compensated for their time (U.S. \$75 after first session, \$125 after second, \$150 after the third, and \$200 after the fourth session).

Participant Safety and Rights

The CBPL staff is trained to ensure that participant safety and rights were maintained throughout the duration of the study. Participants were informed that they may experience some discomfort prior to sessions when they were required to abstain from all nicotine and tobacco products for 12 hours. Side effects from nicotine/tobacco abstinence can include irritability, anxiety, restlessness, excessive hunger, difficulty concentrating, and/or sleep disturbance. Though these side effects can be uncomfortable, they are not medically dangerous nor posed a threat to participants' safety. During study sessions participants were asked to use four products that were different from their usual brand of tobacco cigarettes and were informed of potential side effects that these products may cause; sweating, lightheadedness, dizziness, nausea, and nervousness. Although these side effects could occur, individuals who use tobacco products regularly are unlikely to experience these negative side effects. All subjective analyses, including side effects such as lightheadedness, dizziness, nausea, and nervousness are reported in Table 2.

Participants may have also felt some discomfort when the nurse inserted the IV catheter needle, removed the flexible catheter tube, or when blood samples were taken. The laboratory's trained nurse tried to minimize participants' discomforts at these times and used sterile, disposable equipment that was chosen to enhance comfort and reduce the risk of bruising and infection. These study methods and procedures have been used in this laboratory for over 15 years, and to date, there have been no unanticipated adverse events that have occurred in lab studies of this type. Heart rate and blood pressure were monitored continuously throughout each session and sessions were discontinued if a participant's systolic blood pressure dropped below 90 or elevated above 140, diastolic blood pressure dropped below 60 or elevated above 90, and/or if heart rate dropped below 50 or elevated above 120. If a participant became ill or was

injured from participating in the study, medical treatment would be arranged at the Virginia Commonwealth University Health System, although no participant became ill or was injured during the course of the study.

Potentially identifiable information that was collected about the participants included their name and signature on the consent form, birthdate, and basic demographic information. Consent forms were stored separately from research data. All paper and computer-based research data was identified by an alphanumeric code and stored in locked cabinets in locked rooms that are only accessible by CBPL staff. All computers were password protected. Participants were made aware that if at any time they found any data collection procedures unacceptable or aversive, they could stop their participation without any penalty. Participation was stopped by study staff without consent for reasons that included; participants were not following study instructions (n= 11) or if the study staff believed that it was necessary for participants' health or safety (n = 6). Participants that were discontinued could keep all money earned from the study up to that point.

Materials

During each of the four sessions, participants were provided with a study product; participants' own brand (OB) cigarette, the nicotine inhaler (NICOTROL, Pfizer), an electronic cigarette with nicotine, and an electronic cigarette without nicotine. In the electronic cigarette conditions participants were provided with an "eGo" electronic cigarette, that had a 3.3 volt, 1000 mAh battery and a 1.5 Ohm, dual-coil, 510-style "cartomizer" (SmokTech, Shenzhen, China). The cartomizer was preloaded with 1ml of 70% propylene glycol/ 30% vegetable glycerin flavored e-liquid (tobacco or menthol) that was determined based on participants own brand of cigarette flavor. The two electronic cigarette study sessions differed by nicotine

concentration of the e-liquid; 0mg/ml or 36mg/ml nicotine. E-liquid was purchased from a local electronic cigarette e-liquid vendor, Avail (Richmond, VA) and liquid concentration was verified prior to administration. There was a total of 24 batches of e-liquid used through the course of this study. Results from liquid nicotine verification tests revealed that tobacco and menthol flavored 0 mg/ml nicotine concentration liquids had nicotine levels below the limit of quantification, therefore no traceable amounts of nicotine. The 36 mg/ml nicotine batches had on average 36.21 (SD= 0.5) mg/ml of nicotine in the tobacco flavored e-liquids and on average 35.35 mg/ml (1.2) nicotine in the menthol flavored e-liquid batches.

Outcome Measures

Multiple-Choice Procedure. The Multiple-Choice Procedure (MCP) is a pen and paper task that measures and allows for comparisons of abuse liability between different drugs and drug delivery platforms (Griffiths, Troisi, Silverman, & Miumford, 1993). In the current study, participants were asked to make eleven separate choices (see example in Appendix B, C, and D) between increasing amounts of money and puffs from the study products. After participants made eleven choices between money and puffs, one of their choices was drawn at random by the participant via numbered popsicle sticks. Participants were then presented with their choice immediately, either 10 puffs from the study product (OB, eGo_36, eGo_0, or IN) during a ten-minute period where they take 10 puffs from product ad lib (inter puff interval is not controlled), or the corresponding monetary amount. The total time to finish the ten puffs was recorded. The maximum dollar value that participants choose puffs of the study product over money was the cross-over point. This point was used for the abuse liability analyses. The higher the cross-over value, the greater the reinforcing efficacy of the product. For participants who choose money for all eleven choices, a cross-over point of \$0.00 was used for analysis and for participants who

choose all study product a cross-over point of \$10.24 was used for analysis. The MCP procedure was administered a total of three times with each administration separated by twenty minutes. On average participants received \$4.85 (\$2.38) from the MCP during each session and on average received \$19.42 (\$9.52) from the MCP for all four sessions.

Physiological measures. Immediately after blood collection, samples were centrifuged, and the serum was collected and stored at -70°C until it was sent to VCU's Bioanalytical Analysis Core Laboratories and analyzed for plasma nicotine concentration. The nicotine limit of quantification (LOQ) for the samples was 2ng/ml, for further details regarding blood plasma nicotine analyses see Breland et al, 2006. Participants were connected to Criticare Systems model 507 that monitored heart rate (every 20 seconds) and blood pressure (every four minutes) continuously. Expired CO was measured at the start of every session using the BreathCO monitor (Vitalograph, Lenexa, KS) that was fitted with a disposable mouth piece.

Subjective questionnaires. Four subjective questionnaires were administered at different time points throughout the session: the Hughes and Hatsukami Tobacco Withdrawal Scale, the Direct Effects of Nicotine Questionnaire, the Direct Effects of Product Use Questionnaire, and The Tiffany-Drobes Questionnaire of Smoking Urges. The first and second subjective assessment consisted of the Hughes and Hatsukami Tobacco Withdrawal Scale, the Direct Effects of Nicotine Questionnaire, and the Tiffany-Drobes Questionnaire of Smoking Urges. Subjective assessments three through five consisted of all four subjective questionnaires, and subjective assessments six through eleven consisted of the Hughes and Hatsukami Tobacco Withdrawal Scale only. The subjective questionnaires; Hughes and Hatsukami Tobacco Withdrawal Scale, Direct Effects of Nicotine Scale, and the Direct Effects of Product Scale were administered using a computerized visual analog scale that had a weighted line from "not at all"

on the left to “extremely” on the right. Participants were presented with a word or phrase in the center of the horizontal line and were told to rate how they were currently feeling by using a wireless mouse to click on the line. Scores were calculated by the percentage of the total line length that participants mark from the left anchor. Items from the Tiffany-Drobes Questionnaire of Smoking Urges- Brief were rated on a seven-point Likert scale in which participants clicked seven discrete ratings from ‘not at all’ to ‘extremely’.

Hughes and Hatsukami Tobacco Withdrawal Scale. For this study, an adapted version of the Hughes and Hatsukami Tobacco Withdrawal Scale (Hughes & Hatsukami, 1986) was used to measure tobacco abstinence symptoms (see Breland, Evans, et al., 2002, Buchhalter et al., 2005). This shortened version of the scale consisted of eleven items; “Anxious,” “Craving a cigarette/ nicotine,” “Depression/feeling blue,” “Difficulty concentrating,” “Drowsiness,” “Hunger,” “Impatient,” “Irritability/frustration/anger,” “Restlessness,” “Desire for sweets,” and “Urges to smoke.” The items “Insomnia/disturbed sleep” and “Increased eating” were the items excluded from the shortened version of the scale, as these items were irrelevant during the sessions. This scale was administered a total of 11 times in each session; baseline, before and immediately following the first bout, before and immediately following the second bout, and before and after each of the three MCP choice reinforcements (product puffs or money).

Tiffany-Drobes Questionnaire of Smoking Urges Brief. This subjective questionnaire was modified from the original Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991) and consisted of ten smoking-related items: “I have a desire for a cigarette right now”, “Nothing would be better than smoking a cigarette right now”, “If it were possible, I probably would smoke right now”, “I could control things better right now if I could smoke”, “All I want right now is a cigarette”, “I have an urge for a cigarette”, “A cigarette would taste good now”, “I

would do almost anything for a cigarette now”, “Smoking would make me less depressed”, and “I am going to smoke as soon as possible”. These items were then scored to create two factors: intention to smoke (Factor 1) and anticipation of relief from smoking abstinence (Factor 2; Cox, Tiffany, & Christen, 2001). This scale was administered five times in each session; baseline, before and immediately following the first bout, and before and immediately following the second bout.

Direct Effects of Nicotine Scale. This subjective questionnaire was modified from a previous study (Perkins et al., 1994) and consisted of ten smoking related items that participants rated on a visual analog scale of how they were currently feeling: “Nauseous”, “Dizzy”, “Lightheaded”, “Nervous”, “Sweaty”, “Headache”, “Excessive salivation”, “Heart pounding”, “Confused”, and “Weak” (Evans et al., 2006). This scale was administered five times in each session; Baseline, before and immediately following the first bout, and before and immediately following the second bout.

Direct Effects of Product Scale. This subjective questionnaire was modified from the “Direct Effects of Tobacco” scale that was developed through previous studies evaluating the subjective effects of tobacco cigarette smoking (Buchhalter et al., 2005; Foulds et al., 1992; Pickworth, Bunker, & Henningfield, 1994). This modified scale was generalized for participants to rate the four different study products; “Was the product satisfying?”, “Was the product pleasant?”, “Did the product taste good?”, “Did the product make you dizzy?”, “Did the product calm you down?”, “Did the product help you concentrate?”, “Did the product make you feel more awake?”, “Did the product reduce your hunger for food?”, “Did the product make you sick?”, “Would you like to use another product right now?”. This scale was administered three

times in each session: immediately following the first bout, before the second bout, and immediately following the second bout.

Data Preparation

The FTND (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) was used to estimate participants' cigarette dependence and was used in exploratory analyses examining the influence of cigarette dependence on various study outcome measures. The six items: "How soon after you wake do you smoke your first cigarette?", "Do you find it difficult to refrain from smoking in places where it is forbidden?", "Which cigarette would you most hate to give up?", "How many cigarettes do you smoke each day?", "Do you smoke more during the first few hours after waking up than during the rest of the day?", and "Do you still smoke even if you are so ill that you are in bed most of the day?" are scored and totaled. Scores range from mild dependence (< 4 points) to moderate dependence (4-6 points), and high dependence (7 -10 points).

The MCP crossover point, or the maximum dollar value that participants choose product puffs over money was recorded for each of the three MCP completed by participants. Time during MCP product bouts was recorded and analyzed as an exploratory measure. Blood samples were sent to VCU's Department of Pharmaceutics Bioanalytical Analysis Core Laboratories for blood nicotine concentration analyses (see Breland et al, 2006). The limit of quantification (LOQ) for nicotine concentration was 2ng/ml. Samples that were less than LOQ were rounded up to 2ng/ml for a conservative approach than rounding each data point below the LOQ as zero (as in Vansickel et al., 2010). Physiological data were collected via Criticare Systems model 507 that monitored heart rate (every 20 seconds) and blood pressure (every four minutes) continuously throughout the session. Physiological data points were averaged across time to produce a single value for the baseline and the five minutes during each directed product use

bout. The data points during the washout period (1.5 hours) were divided into two groups (1st half and 2nd half of the washout period) and then average to produce a single data point for the first half and a single data point for the second half. Although heart rate and blood pressure were monitored throughout the remaining two hours of the session, data were not analyzed due to the random nature of selected choices (i.e., puffs of a product or money).

Subjective questionnaires were administered at different time points throughout the session. Due again to lack of interpretability from the random nature of selected choices from the MCP, subjective items after the after the washout period were not analyzed. Only the baseline (T1), pre- (T2) and post (T3)-first product bout, pre- (T4) and post- (T5) second product bout, and post washout period (T6) were included in the general analyses. Exploratory analyses include additional time points, specifically before the MCP administrations (T6, T8, and T10). The Tiffany-Drobes Questionnaire of Smoking Urges-Brief was scored into two factors: intention to smoke (Factor 1) and anticipation of relief from smoking abstinence (Factor 2; Cox, Tiffany, & Christen, 2001). During subjective data cleaning and preparation, a few researcher errors were found in the administration of subjective questionnaires and a few participants did not receive the correct battery of questionnaires at one or more time points and therefore had to be excluded from the subjective analyses. The Hughes and Hatsukami Tobacco Withdrawal Scale was analyzed with all 24 participants, the Tiffany-Drobes Questionnaire of Smoking Urges Brief was analyzed with 21 participants, the Direct Effects of Nicotine Scale was analyzed with 21 participants, and the Direct Effects of Product Scale was analyzed with 22 participants.

Upon receiving initial blood nicotine results from the Bioanalytical Analysis Core Laboratory, plasma nicotine data was inspected to determine if participants were abstinent for at least 12 hours from all nicotine and tobacco products at the start of each study session. Baseline

blood nicotine concentrations were examined for blood plasma nicotine concentrations over 5.0 ng/ml, as these participants were not considered abstinent (see Hiler et al., 2017; Spindle et al., 2016). A total of ten participants had at least one session with baseline plasma nicotine concentrations over the 5.0 ng/ml cut-off deemed as not abstinent. Abstainers and non-abstainers were dichotomized and each outcome measure was analyzed as described below.

Data Analysis Plan

The statistical analyses for the outcome measures were performed using IBM SPSS (Version 23.0). For the MCP crossover points, a four (product) by three (time) within-subjects ANOVA was performed to test for differences in crossover point between the study products. For plasma nicotine levels, a four (product) by four (time) within-subjects ANOVA was performed to test for differences in nicotine delivery between the study products. The subjective effects questionnaire items were analyzed using within-subjects, repeated measures ANOVAs. Analyses for subjective effects were conducted only with subjective data preceding the MCP due to differing choices and selections made by participants after MCP administration, making data interpretation difficult. Thus, items from the Hughes and Hatsukami Tobacco Withdrawal Scale were analyzed using a four (product) by 6 (time) repeated measures ANOVA. Items from the Tiffany-Drobes Questionnaire of Smoking Urges-Brief factors were analyzed using a four (product) by five (time) repeated measures ANOVA. Items from the Direct Effects of Nicotine Scale were analyzed using a four (product) by five (time) repeated measures ANOVA. Finally, items from the Direct Effects of Product Scale were analyzed using a four (product) by three (time) repeated measures ANOVA. Repeated measures ANOVAs are often inclined to violate the assumptions of sphericity increasing the likelihood of making a Type 1 error. Sphericity violations occur when the difference between each related condition's variances are unequal.

Violations of sphericity were tested using Mauchly's Test of Sphericity (Mauchly et al., 1940) and any violations were corrected using the Huynh-Feldt correction (Huynh & Feldt, 1976) that adjusted the degrees of freedom in order to obtain a valid critical *F*-value. Significant interactions and main effects were analyzed using planned contrasts. Specifically, Bonferroni-corrected paired-samples t-tests were conducted to examine differences from baseline for measures with a true baseline (i.e., blood plasma nicotine concentration, blood pressure, heart rate, and all subjective measures except the Direct Effects of Product). Bonferroni-corrected paired samples t-tests were also used to examine differences between own brand cigarettes and the electronic cigarette with nicotine and the electronic cigarette without nicotine, and to compare the inhaler to the electronic cigarette with nicotine and the electronic cigarette without nicotine. Comparisons between the own brand cigarette condition and the inhaler condition were not made due to previous research establishing that these products have high and low abuse liability (Henningfield & Keenan 1993; Hughes 1998; West et al., 2000).

The effect of abstinence status was examined before the aforementioned analyses using mixed factorial ANOVAs with abstinence status a between-subjects factor (i.e., abstinent or non-abstinent) and condition (i.e., product) and time levels for the outcome measures (i.e., MCP, blood plasma nicotine concentrations, physiological measures, and subjective measures) as within-subject's factors. Post-hoc tests were conducted on any variables with a significant effect of abstinence status. There were a total of five outcome measures (all subjective items; i.e., "Craving a cigarette/nicotine", "Urges to smoke", "Calm", "Dizzy", and "Taste good") that had an effect of abstinence status, further described in the results below.

Exploratory analyses were conducted to assess differences between the 0 and 36 mg/ml nicotine electronic cigarette conditions using paired samples t-tests. Additional exploratory

Bonferroni-corrected paired samples t-tests were conducted to examine differences in consumption rates and differences between liquid flavors. Finally, correlations were conducted on participant dependence scores and MCP choices, product consumption rates, and subjective measures to examine the influence of nicotine dependence on these measures of product abuse liability.

Results

This within-subjects, double-blind, clinical laboratory study examined the abuse liability of an electronic cigarette filled with liquid containing 0 mg/ml nicotine (eGo_0) and an electronic cigarette filled with liquid containing 36 mg/ml nicotine (eGo_36) and compared these products to participants' own brand of cigarettes (OB) and to a 4mg nicotine inhaler (IN). Statistical analyses (interactions and main effects) for all outcome measures can be found in Table 2. Interactions of condition and time and main effects of condition were of greatest interest as they highlight differences in aspects of abuse liability between the study products.

Table 2.

Summary of Results for All Outcome Measures.

Outcome Measure	Condition			Time			Condition × Time		
	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2
MCP	9.75	<.001	.30	1.96	<i>ns</i>	.08	0.74	<i>ns</i>	.03
Plasma Nicotine	21.51	<.001	.48	32.92	<.001	.59	10.849	<.001	.32
HR	6.946	<.001	.23	51.02	<.001	.69	12.36	<.001	.35
Systolic BP	8.44	<.001	.27	2.44	<i>ns</i>	.10	1.26	<i>ns</i>	.05
Diastolic BP	8.87	<.001	.28	6.42	<.001	.22	2.41	<.05	.095
Subjective Measures									
Hughes-Hatsukami ^a									
Anxious	1.55	<i>ns</i>	.06	8.20	<.001	.26	2.90	<.05	.09
Craving	11.02	<.001	.32	12.40	<.001	.35	6.80	<.001	.23
Depression	.91	<i>ns</i>	.04	.47	<i>ns</i>	.02	1.59	<i>ns</i>	.06
Difficulty concentrating	1.88	<i>ns</i>	.08	2.34	<i>ns</i>	.09	.73	<i>ns</i>	.03
Drowsy	1.18	<i>ns</i>	.05	1.95	<i>ns</i>	.08	1.87	<i>ns</i>	.08
Hunger	1.70	<i>ns</i>	.07	5.83	<.01	.20	1.13	<i>ns</i>	.07
Impatient	2.00	<i>ns</i>	.08	6.39	<.001	.22	1.91	<.05	.07
Irritable	.48	<i>ns</i>	.02	6.21	<.01	.21	1.12	<i>ns</i>	.05
Restless	2.84	<i>ns</i>	.11	2.97	<.05	.11	1.39	<i>ns</i>	.06
Sweets	.90	<i>ns</i>	.04	1.30	<i>ns</i>	.05	1.28	<i>ns</i>	.05
Urge	7.51	<.001	.25	17.98	<.001	.44	3.337	<.01	.13
Tiffany-Drobes ^b									
Factor 1	9.18	<.001	.32	16.90	<.001	.46	8.71	<.001	.30
Factor 2	2.25	<i>ns</i>	.10	6.31	<.05	.24	4.40	<.01	.18
Direct effects of nicotine ^c									
Confused	.18	<i>ns</i>	.01	.83	<i>ns</i>	.04	1.18	<i>ns</i>	.06
Dizzy	2.65	<i>ns</i>	.12	3.41	<.05	.15	2.15	<i>ns</i>	.10
Headache	.41	<i>ns</i>	.02	.73	<i>ns</i>	.04	1.17	<i>ns</i>	.06
Heart pound	1.05	<i>ns</i>	.05	1.84	<i>ns</i>	.08	1.19	<i>ns</i>	.06
Light headed	5.62	<.01	.22	5.14	<.01	.205	2.61	<.05	.12
Nausea	1.34	<i>ns</i>	.06	.12	<i>ns</i>	.01	1.19	<i>ns</i>	.06
Nervous	.19	<i>ns</i>	.01	2.01	<i>ns</i>	.09	.80	<i>ns</i>	.04
Salivate	.13	<i>ns</i>	.01	1.98	<i>ns</i>	.09	.48	<i>ns</i>	.02
Sweaty	.220	<i>ns</i>	.01	5.44	<.01	.21	.77	<i>ns</i>	.04
Weak	1.02	<i>ns</i>	.05	.34	.76	.02	.63	<i>ns</i>	.03
Direct effects of product use ^d									
Awake	15.45	<.001	.42	6.71	<.01	.24	1.49	<i>ns</i>	.07
Calm	14.86	<.001	.41	11.43	<.001	.35	2.26	<.05	.10
Concentrate	11.49	<.001	.35	.07	<i>ns</i>	.00	.54	<i>ns</i>	.03
Dizzy	8.16	<.001	.28	2.76	<i>ns</i>	.12	1.74	<i>ns</i>	.08
Pleasant	34.26	<.001	.62	4.59	<.05	.18	1.81	<i>ns</i>	.08
Reduced hunger	9.54	<.001	.31	1.20	<i>ns</i>	.05	.87	<i>ns</i>	.04
Right now	.59	<i>ns</i>	.03	5.70	<.01	.21	1.81	<i>ns</i>	.08
Satisfy	44.20	<.001	.68	2.54	<i>ns</i>	.11	2.11	<i>ns</i>	.09
Sick	1.05	<i>ns</i>	.05	.23	<i>ns</i>	.01	.64	<i>ns</i>	.03
Taste good	40.48	<.001	.66	3.87	<.05	.16	1.96	<i>ns</i>	.09

Note. ^a Hughes and Hatsukami Tobacco Withdrawal Scale, ^b Tiffany-Drobes Questionnaire of

Smoking Urges Brief, ^c Direct Effects of Nicotine Use, and ^d Direct Effects of Product Use.

Multiple-Choice Procedure

A significant main effect of condition [$F(3, 69) = 9.75, p < .001$] was observed for the MCP crossover point. Collapsed across time, the mean MCP crossover point for the OB condition was \$1.42 (SD = 1.4) and was significantly higher than the mean of the eGo_36 condition that was \$0.87 (1.0), [$t(23) = 3.27, p < .05$]. The mean crossover point of \$1.42 (1.4) in the OB condition was not significantly different from the eGo_0 condition that had a mean of \$0.96 (1.2), [$t(23) = 2.35, p > .025$]. The mean MCP crossover point for the IN condition was \$0.32 (0.6), which was significantly lower than the eGo_36 condition's mean of \$0.87 (1.0) and the eGo_0 condition's mean of \$0.96 (1.2), [$ts > 2.71, ps < .025$]. Exploratory analyses did not reveal a significant difference between eGo_0 and eGo_36. Figure 2 shows the mean crossover point for each condition.

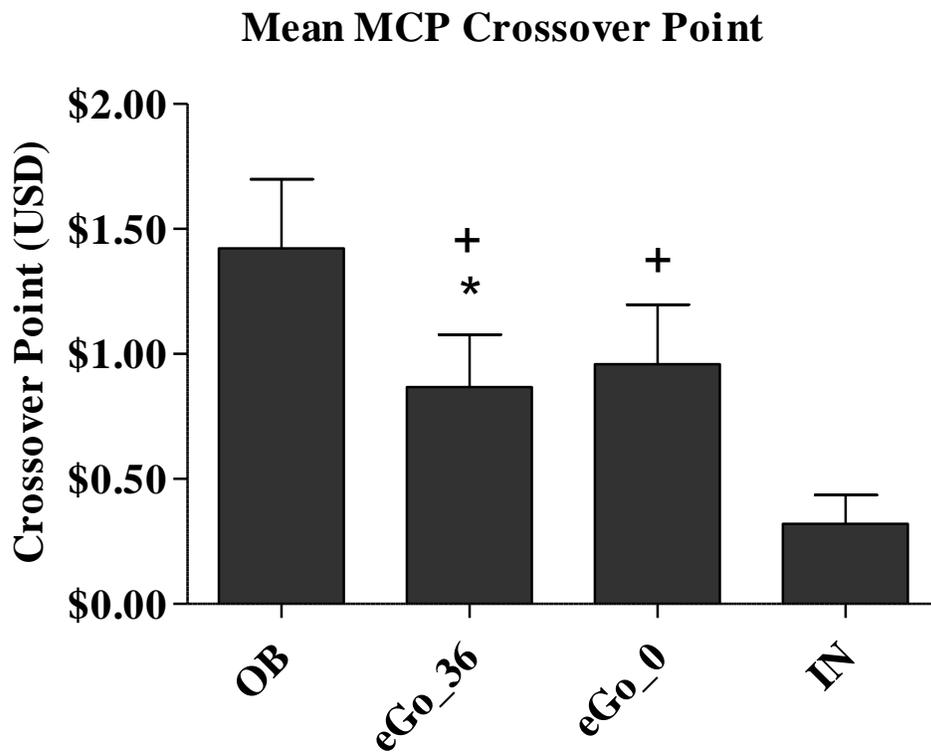


Figure 2. Mean (+SEM) for the average MCP crossover point across conditions for 24 electronic cigarette naïve smokers. Asterisks (*) indicate significant difference from OB and plus sign (+) indicates a significant difference from IN (t -test, $ps < .05$).

Physiological Measures

Plasma nicotine. A significant condition by time interaction [$F(9, 207) = 10.85, p < .001$], and significant main effects of condition [$F(3, 69) = 21.51, p < .001$] and time [$F(3, 69) = 32.92, p < .001$] were observed for plasma nicotine concentration. Mean plasma nicotine concentrations increased in the OB condition from 3.55 ng/ml (2.8) at baseline to 13.64 ng/ml (9.8) following the first bout and to 14.86 (8.6) ng/ml following the second bout [$t_s > 4.62, p_s < .001$]. Compared to baseline plasma nicotine levels, the mean plasma nicotine concentration remained elevated in the OB condition at 8.26 ng/ml (5.5) following the washout period [$t(23) = -3.26, p < .01$]. Mean blood plasma nicotine concentrations increased in the eGo_36 condition from 3.16 ng/ml (1.8) at baseline to 8.51 ng/ml (5.4) following the first bout and to 11.29 (8.8) ng/ml following the second bout [$t_s > 4.50, p_s < .001$]. Compared to baseline plasma nicotine levels, the mean plasma nicotine concentration remained elevated in the eGo_36 condition at 6.29 ng/ml (3.4) following the washout period [$t(23) = -4.50, p < .001$]. There were no significant elevations in plasma nicotine concentration in the eGo_0 or the IN condition, indicating that plasma nicotine concentrations remained low throughout the session in these two conditions [$t_s > -2.28, p_s > .017$].

There were no significant differences in plasma nicotine levels between conditions at baseline, although significant differences were also observed across conditions at later time points. Following the first 10-puff product bout, the mean plasma nicotine concentration in the OB condition was 13.64 ng/ml (9.9), significantly higher than the eGo_0 condition in which participants had a mean plasma nicotine concentration of 3.29 ng/ml (1.9), [$t(23) = 5.01, p < .001$]. Similar results were observed after the second bout, in that the participant's mean plasma nicotine concentration in the OB condition was 14.87 ng/ml (8.7), significantly higher than the

eGo_0 condition where participants had a mean plasma nicotine concentration of 3.06 ng/ml (1.6), [$t(23) = 6.14, p < .001$]. Participants' mean plasma nicotine concentration in the OB condition was 8.26 ng/ml (5.5) following the washout period and was significantly higher than the eGo_0 condition in which participants had a mean plasma nicotine concentration of 3.10 ng/ml (1.5) following the washout period [$t(23) = 4.29, p < .001$].

Following the first 10-puff product bout, the mean plasma nicotine concentration in the IN condition was 4.26 ng/ml (2.8), significantly lower than the eGo_36 condition in which participants had a mean plasma nicotine concentration of 8.51 ng/ml (5.4), [$t(23) = -3.25, p < .01$]. Similar results were seen after the second bout, in that the mean plasma nicotine in the IN condition was 4.66 ng/ml (2.4), significantly lower than in the eGo_36 condition where a mean plasma nicotine concentration of 11.29 ng/ml (8.8) was observed [$t(23) = -3.81, p < .01$].

Following the second 10-puff product bout, the mean plasma nicotine concentration in the IN condition was 4.66 ng/ml (2.4), significantly higher than levels in the eGo_0 condition, which were 3.06 ng/ml (1.6), [$t(23) = 3.64, p < .01$]. Following the washout period, mean plasma nicotine concentration in the IN condition was 4.64 ng/ml (2.6) and was significantly higher than in the eGo_0 condition, which was 3.10 ng/ml (1.5), [$t(23) = 2.62, p < .05$].

Exploratory analyses between eGo_36 and eGo_0 condition revealed that in the eGo_36 condition, participants had a significantly higher mean plasma nicotine concentration of 8.51 ng/ml (5.4) than the eGo_0 condition, in which mean plasma nicotine concentration was 3.29 ng/ml (1.9) following the first bout [$t(23) = -4.73, p < .001$]. Similar results were found following the second bout in that the eGo_36 condition, participants had a significantly higher mean plasma nicotine concentration of 11.29 ng/ml (8.8) than the eGo_0 mean, in which participants' mean plasma nicotine concentration was 3.06 ng/ml (1.6) following the first bout [t

(23) = -4.60, $p < .001$]. Finally, participants' mean plasma nicotine concentrations remained elevated in the eGo_36 condition at 6.29 ng/ml (3.4) compared to the participants mean plasma nicotine concentrations that was 3.10 ng/ml (1.5) in the eGo_0 condition following the washout period [$t(23) = -4.68, p < .001$]. Figure 3 depicts plasma nicotine levels over time and by condition.

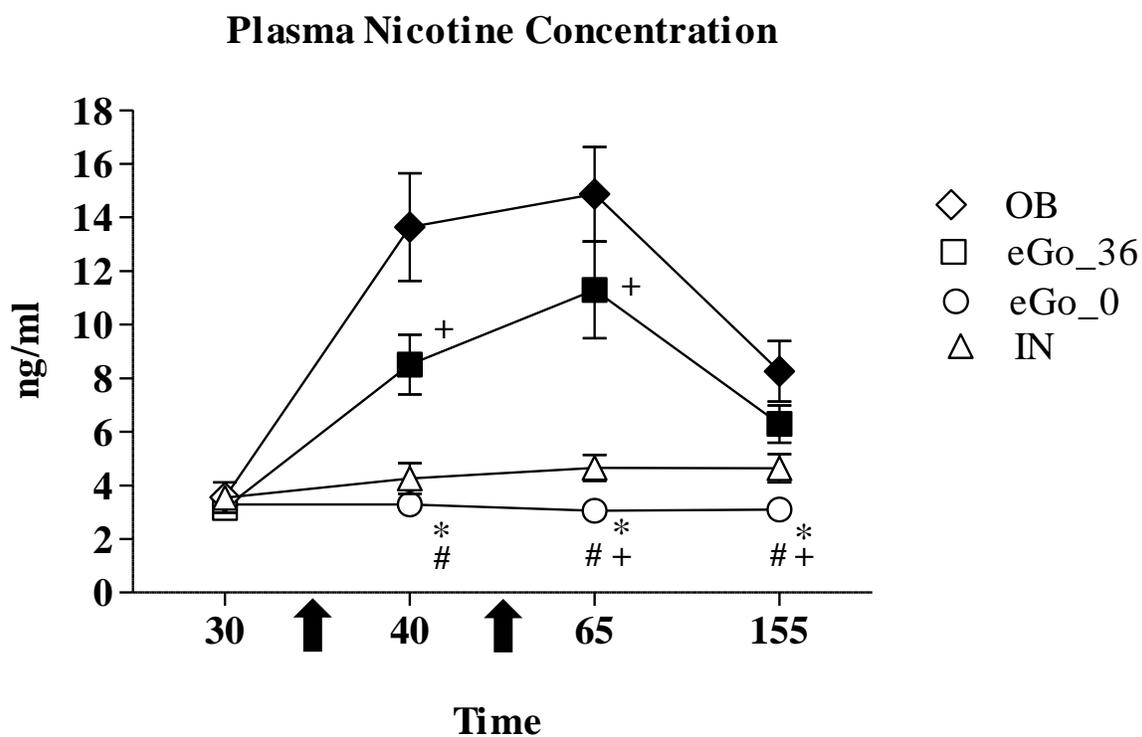


Figure 3. Mean (\pm SEM) for plasma nicotine concentration for 24 electronic cigarette naïve smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline. Asterisks (*) indicates a significant difference from OB, plus sign (+) indicates significant difference from IN, and (#) pound symbol indicates significant difference from eGo_36 at that time-point for that product (*t*-test).

Heart rate. A significant condition by time interaction [$F(12, 276) = 12.36, p < .001$], and significant main effects of condition [$F(3, 69) = 6.95, p < .001$] and time [$F(4, 92) = 51.02, p < .001$] were observed for heart rate. Participants' mean heart rate in the OB condition significantly increased from a baseline mean of 67.08 bpm (8.2) to 79.16 bpm (8.2) during the first bout and to 77.73 bpm (7.9) during the second bout [$t_s > 7.76, p_s < .001$]. Participants' mean heart rate levels during the first half of the washout period in the OB condition was 72.32 bpm (8.4), significantly higher than baseline [$t(23) = -4.62, p < .001$]. Participants' mean heart rate in the eGo_36 condition significantly increased from a baseline mean heart rate of 67.54 bpm (9.59) to 72.59 bpm (8.6) during the first bout and remained higher at a mean heart rate of 71.37 bpm (8.3) during the second bout [$t_s > 3.92, p_s < .01$]. Participants' mean heart rate in the eGo_0 condition significantly decreased from a baseline mean of 70.25 bpm (9.7) to 64.86 bpm (8.2) during the first part of the washout period and to 63.38 bpm (8.1) during the second part of the washout period [$t_s > 5.17, p_s < .001$]. Participants' mean heart rate in the IN condition significantly increased from a baseline mean of 67.71 bpm (12.0) to 69.74 bpm (11.7) during the first bout [$t(23) = -3.06, p < .01$]. Participants mean heart rate levels in the IN condition was 64.43 bpm (11.8) during the second half of the washout period was significantly lower than their baseline heart rate [$t(23) = 3.36, p < .01$].

There were no significant differences in heart rate between conditions at baseline, although significant differences were also observed across conditions at later time points. During the first bout, participants had a mean heart rate of 79.16 bpm (8.2) in the OB condition that was significantly higher than participants' mean heart rate in the eGo_36 condition that was 72.59 bpm (8.6) and participants' mean heart rate in the eGo_0 condition that was 71.45 bpm (8.3), [$t_s > 3.71, p_s < .01$]. Similar results were found during the second bout, such that participants had a

significantly higher mean heart rate of 77.73 bpm (7.9) in the OB condition compared to 71.37 bpm (8.3) in the eGo_36 condition and 69.29 bpm (7.9) in the eGo_0 condition [$t_s > 3.84$, $p_s < .01$]. Participants' mean heart rate in the OB condition was 72.32 bpm (8.4) in the first half of the washout period, significantly higher than participants' mean heart rate of 68.24 bpm (8.5) in the eGo_36 condition and participants' mean heart rate of 64.86 bpm (8.9) in the eGo_0 condition [$t_s > 2.72$, $p_s < .025$]. Participants' mean heart rate of 68.35 bpm (6.8) in the OB condition remained higher during the second half of the washout period than participants' mean heart rate of 64.86 bpm (8.2) in the eGo_0 condition [$t(23) = 3.35$, $p < .01$]. Participants' heart rate in the IN condition was 67.47 bpm (10.8), significantly lower during the second bout than participants mean heart rate in the eGo_36 condition of 71.37 bpm (8.3), [$t(23) = -2.67$, $p < .025$].

Exploratory analyses between the eGo_36 condition and the eGo_0 condition did not reveal any significant differences in heart rate at baseline, during the first bout, during the second bout, or during the washout period. Figure 4 depicts heart rate levels over time and by condition.

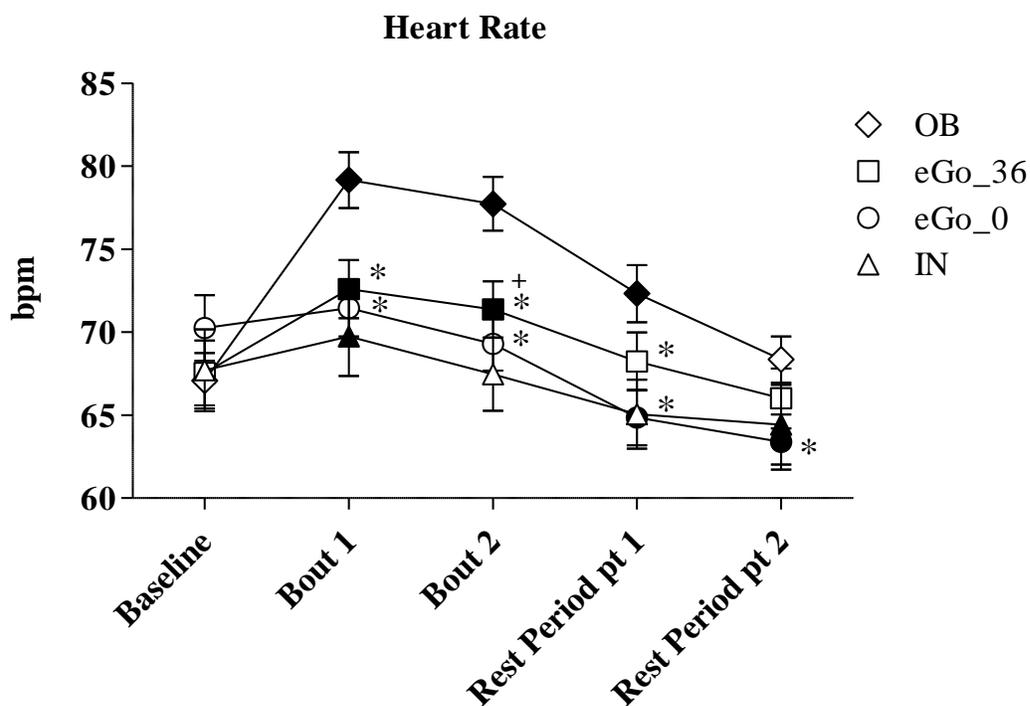


Figure 4. Mean (\pm SEM) for heart rate in bpm (i.e., beats per minute) for 24 electronic cigarette naïve smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline at that time point. Asterisks (*) indicates a significant difference from OB, plus sign (+) indicates significant difference from IN, and (#) pound symbol indicates significant difference from eGo_36 at that time-point for that product (t -test, $ps < .05$).

Systolic blood pressure. A significant main effect of condition [$F(3, 69) = 8.44, p < .001$] was observed for systolic blood pressure. At baseline, participants' mean systolic blood pressure was 118.17 mmHg (9.5) in the eGo_36 condition, significantly lower than in the IN condition mean of 121.64 mmHg (9.0), [$t(23) = -2.94, p < .008$]. No other significant baseline differences were observed. Collapsed across time, participants mean systolic blood pressure was 126.74 mmHg (7.6) in the OB condition, significantly higher compared to a mean of 120.46 mmHg (8.2) in the eGo_36 condition and a mean of 120.39 mmHg (9.0) in the eGo_0 condition [$ts > 4.25, ps < .001$]. No other significant differences were observed for systolic blood pressure.

Diastolic blood pressure. A significant condition by time interaction [$F(12, 276) = 2.41, p < .05$], and significant main effects of condition [$F(3, 69) = 8.87, p < .001$] and time [$F(4, 92) = 6.42, p < .001$] were observed for diastolic blood pressure. Participants' mean diastolic blood pressure in the OB condition significantly increased from a baseline mean of 73.15 mmHg (6.6) to 82.44 mmHg (6.8) during the first bout [$t(23) = 5.48, p < .001$]. Participants' mean diastolic blood pressure in the eGo_36 condition was 70.28 mmHg (6.3) at baseline, significantly lower compared to 74.37 mmHg (7.4) during the second half of the washout period [$t(23) = -3.27, p < .01$]. In the eGo_0 condition, participants' mean diastolic blood pressure during was 72.08 mmHg (7.5) at baseline, significantly lower compared to the second bout which was 76.29 mmHg (9.6) [$t(23) = -3.09, p < .01$]. No other significant changes from baseline were observed.

At baseline, there was a significant difference between the eGo_36 and the IN condition in baseline blood pressure, [$t(23) = -2.94, p < .01$]. Participants had a lower mean diastolic blood pressure at baseline of 118.2 mmHg (9.5) in the eGo_36 condition compared to the mean of 121.6 (9.0) in the IN condition. No other significant differences were observed between conditions at baseline. Participants in the OB condition had a mean diastolic blood pressure of

82.44 mmHg (6.8) during the first bout, significantly higher compared to the eGo_36 condition's mean of 72.96 mmHg (6.0) and the eGo_0 condition's mean of 73.44 mmHg (8.6) during the first bout [$t_s > 4.82, p_s < .001$]. During the second product bout, participants in the IN condition had a mean diastolic blood pressure that was 70.54 mmHg (9.3), significantly lower compared to the eGo_0 condition mean of 76.29 mmHg (9.6), [$t(23) = -2.85, p < .01$]. Finally, during the second half of the washout period a mean diastolic blood pressure of 70.75 mmHg (7.0) was observed in the IN condition, significantly lower compared to a mean of 74.37 mmHg (7.4) observed in the eGo_36 condition [$t(23) = -2.68, p < .05$]. No significant differences were observed between eGo_36 and the eGo_0 conditions. Figure 5 depicts diastolic blood pressure levels over time and by condition.

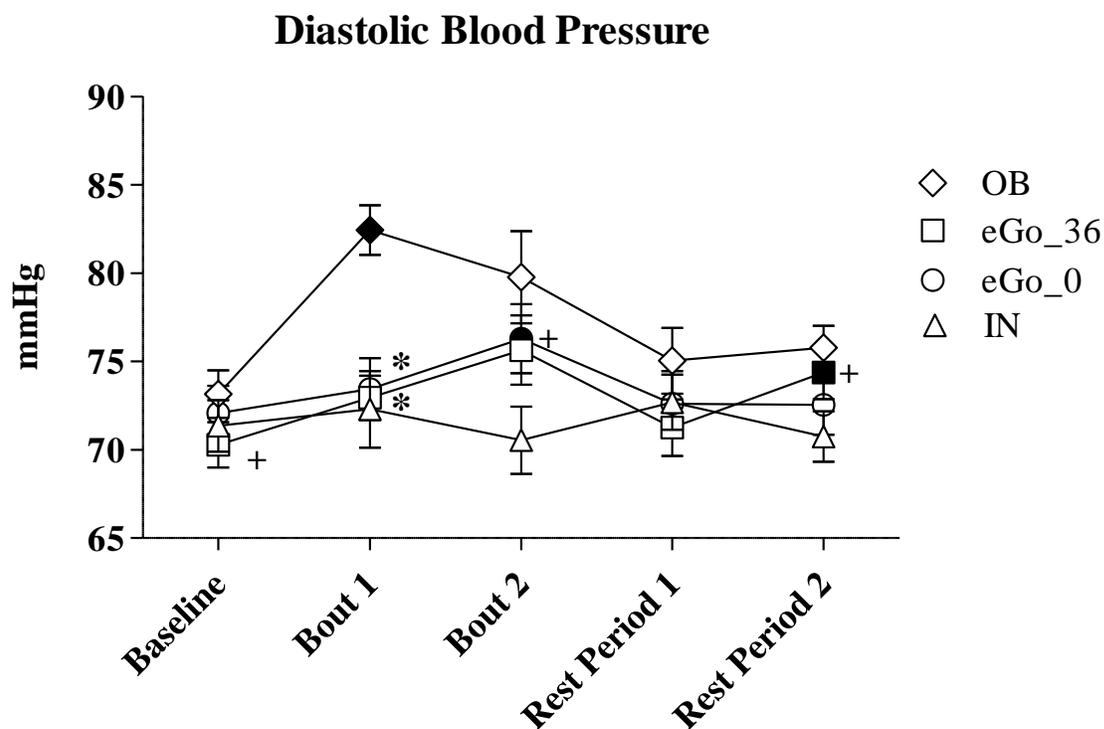


Figure 5. Mean (\pm SEM) for diastolic blood pressure for 24 electronic cigarette naïve smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline at that time point. Asterisks (*) indicates a significant difference from OB and plus sign (+) indicates significant difference from IN at that time-point for that product (*t*-test).

Subjective Measures

Hughes and Hatsukami Tobacco Withdrawal Scale. Significant condition by time interactions were observed for the items “Anxious”, “Craving a cigarette/nicotine”, “Impatient”, and “Urges to smoke” [$F_s > 1.91, p_s < .05$]. Significant main effects of condition were observed for the items “Craving a cigarette/nicotine” and “Urges to smoke” [$F_s > 7.51, p_s < .001$] and significant main effects of time were observed for the items “Anxious”, “Craving a cigarette/nicotine”, “Hunger”, “Impatient”, and “Urges to smoke” [$F_s > 5.83, p_s < .01$]. Figure 6 shows the results for “Craving a cigarette/nicotine” figure 7 show the results for “Urges to smoke” (two of the items with the largest F values).

Anxious. A significant condition by time interaction [$F(15, 345) = 2.29, p < .05$], and a main effect of time [$F(5, 115) = 8.20, p < .001$] were observed for the item “Anxious”. Participants’ mean rating of “Anxious” was significantly reduced in the OB condition from a mean of 34.00 (37.4) at baseline to 14.63 (24.6) after the first bout and to 12.54 (23.8) after the second bout, and their mean rating remained lower at 18.92 (30.5) following the washout period [$t_s > 2.99, p_s < .01$]. Participants’ mean rating of “Anxious” was significantly reduced in the eGo_36 condition from 41.50 (40.4) at baseline to 10.96 (15.3) after the first bout and to 21.71 (32.3) after the second bout, [$t_s > 2.94, p_s < .01$].

There were no significant differences across conditions were observed for the item “Anxious” at baseline, although significant differences were also observed across conditions at later time points. In the OB condition, participants had lower mean rating of “Anxious” that was 18.92 (30.5) following the washout period than in the eGo_36 condition that had a mean rating of 30.25 (36.1) following the washout period, [$t(23) = -2.57, p < .025$]. Exploratory analyses

revealed no significant differences in participants mean ratings of the item “Anxious” between the eGo_36 and the eGo_0 conditions.

Craving a cigarette/nicotine. A significant condition by abstinence status interaction was observed for the item “craving a cigarette/nicotine” [$F(3, 66) = 3.08, p < .05$]. Post-hoc independent t-tests revealed that collapsed across time, in the OB condition, abstinent participants ($n=14$) had a higher mean rating of craving of 64.68 (19.0) than non-abstinent participants ($n = 10$) who had a mean of 35.48 (25.8), [$t(23) = 3.20, p < .01$]. No other significant differences between abstinent and non-abstinent participants in the eGo_36, eGo_0, or IN conditions were observed for the item “craving a cigarette”. Separate analyses for abstinent and non-abstinent participants revealed a similar interaction for abstinent [$F(15, 195) = 3.50, p < .001$] and non-abstinent participants [$F(15, 135) = 4.30, p < .001$], a similar main effect of condition for abstinent [$F(3, 39) = 4.69, p < .01$] and non-abstinent participants [$F(3, 27) = 7.58, p < .01$], and a similar main effect of time for abstinent [$F(5, 65) = 9.20, p < .01$] and non-abstinent participants [$F(5, 45) = 4.37, p < .05$]. Therefore, because the overall pattern of results was similar between abstinent and non-abstinent participants, the data were collapsed across abstinence status and all participant data were analyzed together.

Collapsed across abstinence status, a significant condition by time interaction [$F(15, 345) = 6.80, p < .001$], and main effects of condition [$F(3, 69) = 11.02, p < .001$] and time [$F(5, 115) = 12.40, p < .001$] were observed for the item “Craving a cigarette/nicotine”. Participants’ mean rating of “Craving a cigarette/nicotine” was significantly reduced in the OB condition from 72.08 (33.4) at baseline to 37.71 (31.8) after the first bout, remained lower at 52.63 (36.2) after the 20-minute rest period (before the second bout), was reduced further to 25.42 (27.7) after the second bout, and their mean rating remained lower than baseline at 52.25 (32.3) following the

washout period [$t_s < 2.81$, $p_s < .05$]. Participants' mean rating was significantly reduced in the eGo_36 condition from 78.58 (28.2) at baseline to 55.63 (37.6) after the first bout, remained lower than baseline at 65.21 (32.5) after the 20-minute rest period (before the second bout), and was reduced again following the second bout to 56.08 (38.8), [$t_s > 2.98$, $p_s < .01$]. No other significant changes from baseline were observed.

There were no significant differences in "Craving a cigarette/nicotine" between conditions at baseline, although significant differences were also observed across conditions at later time points. Following the first bout, participants' mean rating for this item was 37.71 (31.8) in the OB condition, significantly lower than in the eGo_36 condition that had a mean rating of 55.63 (37.6), and the eGo_0 condition that had a mean rating of 67.25 (35.5), [$t_s > 2.51$, $p_s < .05$]. Following the second bout, participants' mean rating was 25.42 (27.7) in OB condition, significantly lower than their mean rating of 56.08 (38.8) in the eGo_36 condition and their mean rating of 66.67 (35.1) in the eGo_0 condition [$t_s > 3.75$, $p_s < .01$]. Participants' mean rating of this item was 52.25 (32.3) in the OB condition following the washout period, significantly lower than their mean rating of 74.00 (25.2) observed in the eGo_36 condition and their mean rating of 75.79 (30.9) observed in the eGo_0 condition [$t_s > 3.74$, $p_s < .01$]. In the inhaler condition, participants' mean rating of this item was 73.88 (30.9) following the first bout, significantly higher than the mean rating observed in the eGo_36 condition of 55.63 (37.6), [$t(23) = 2.48$, $p < .05$]. Following the second bout, participants' mean rating of this item was 76.38 (32.1) in the IN condition, significantly higher than their mean rating of 56.08 (38.80) observed in the eGo_36 condition [$t(23) = 2.90$, $p < .01$]. Exploratory analyses did not reveal any significant differences between the eGo_36 and the eGo_0 conditions. Figure 6 depicts subjective ratings of "craving a cigarette/nicotine" over time and by condition.

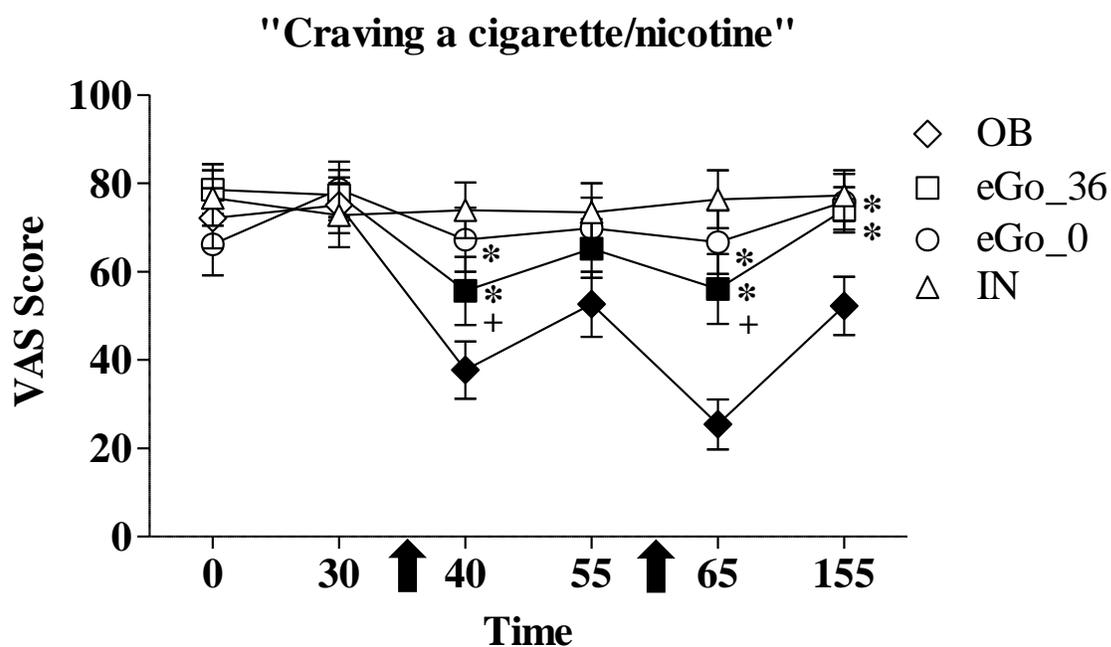


Figure 6. Mean (\pm SEM) for VAS score of craving and urge from 24 electronic cigarette naïve smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline at that time point. Asterisks (*) indicates a significant difference from OB and plus sign (+) indicates significant difference from IN at that time-point for that product (*t*-test).

Impatient. A significant condition by time interaction [$F(15, 345) = 1.91, p < .05$] and a main effect of time [$F(5, 115) = 6.39, p < .001$] was observed for the item “Impatient”. Participants’ mean rating of the item “impatient” in the OB condition was 28.00 (32.0) at baseline, and was significantly reduced following the second bout to 8.25 (12.7), [$t(23) = 3.33, p < .01$]. No other significant changes from baseline were observed.

At baseline, there was a significant difference between the eGo_0 and the IN condition, [$t(23) = 2.32, p < .05$]. Participants had a lower mean rating of 20.58 (23.8) at baseline in the eGo_0 condition compared to a mean of 32.75 (33.4) in the IN condition. No other significant differences were observed between conditions at baseline. Before the second bout, participants’ mean rating of 24.42 (30.9) in the IN condition was significantly higher than participants’ mean rating of 13.46 (20.2) in the eGo_36 condition, [$t(23) = 2.75, p < .05$]. Following the second bout, participants in the OB condition had a mean rating of 8.25 (12.7) for the item “impatient” that was significantly lower than their mean rating in the eGo_0 condition that was 20.08 (25.9), [$t(23) = 2.56, p < .05$]. Exploratory analyses revealed a significant difference between eGo_36 and the eGo_0 condition following the 20-minute rest period, prior to the second bout. Participants in the eGo_36 condition had a mean rating of 13.46 (20.2) that was significantly lower than their mean rating of 24.46 (28.0) in the eGo_0 condition [$t(23) = -2.78, p < .05$].

Urges to smoke. A significant condition by abstinence status interaction was observed for the item “Urges to smoke” [$F(3, 66) = 3.35, p < .05$]. Post hoc tests revealed that there was significant difference between participants who abstained and participants who did not abstain in the OB condition [$t(22) = 2.77, p < .05$]. More specifically, collapsed across time, participants who abstained had a higher mean rating that was 69.07 (18.1) on this item, higher than participants who did not abstain who had an overall mean rating of 38.35 (25.7), [$t(22) = 3.44, p$

< .01]. Separate analyses for abstinent and non-abstinent participants did not reveal a significant interaction for abstinent participants [$F(15, 195) = 1.42, p > .05$] but did for non-abstinent participants [$F(15, 135) = 3.18, p < .01$]. There was not a main effect of condition observed for abstinent participants [$F(3, 39) = 2.16, p > .05$] but there was for non-abstinent participants [$F(3, 27) = 6.60, p < .01$]. However, there was a similar main effect of time that was observed for abstinent participants [$F(5, 65) = 10.52, p < .01$] and non-abstinent participants [$F(5, 45) = 7.45, p < .01$]. Although statistical analyses revealed differences between abstinent and non-abstinent participants, our study is not adequately powered to detect effects of product condition when participants are grouped by abstinence status. Because the primary focus of this study is to examine the effects of products and not abstinence status, participants were collapsed across abstinence status to adequately power post-hoc analyses examining the effects of products.

Collapsed across abstinence status, a significant condition by time interaction was observed for the item “Urges to smoke” [$F(15, 345) = 3.37, p < .01$], as well as main effects of condition [$F(3, 69) = 7.51, p < .001$] and time [$F(5, 115) = 17.98, p < .001$]. Participant ratings of “Urges to smoke” decreased significantly in the OB condition from a mean baseline rating of 74.21 (32.1) to a rating of 43.54 (31.6) after the first bout, remained lower with a mean rating of 54.42 (35.3) following the 20-minute rest period, further decreased to 31.38 (30.6) following the second bout, and remained significantly lower than baseline following the 1.5-hour washout period with a mean rating of 60.04 (28.7), [$ts > 3.32, ps < .01$]. Participant ratings of “Urges to smoke” decreased significantly in the eGo_36 condition from a baseline rating of 80.42 (26.3) to a rating of 56.17 (36.8) after the first bout, to a mean rating of 64.63 (33.5) following the 20-minute rest period, and a mean rating of 56.21 (37.8) following the second bout [$ts > 2.61, ps < .01$].

There were no significant differences in “Urges to smoke” between conditions at baseline, although significant differences were also observed across conditions at later time points. Following the first bout, participants had a mean rating of “Urges to smoke” of 43.54 (31.6) in the OB condition that were significantly lower than their mean rating of 64.00 (35.1) in the eGo_0 condition, [$t(23) = -2.45, p < .025$]. Following the 20-minute rest period (prior to the second bout), participants had a mean rating of 52.42 (35.3) in the OB condition that was significantly lower than their mean rating of 72.46 (34.3) in the eGo_0 condition, [$t(23) = -2.56, p < .025$]. Following the second bout, participants had a mean rating of 31.38 (30.6) in the OB condition that was significantly lower than the mean rating of 56.21 (37.8) in the eGo_36 condition and 64.92 (38.4) in the eGo_0 condition, [$t_s > 2.69, p_s < .025$]. There were no significant differences between IN and eGo_36 and eGo_0 conditions. Exploratory analyses did not reveal any significant differences between participants ratings of “Urges to smoke” in the eGo_36 and the eGo_0 conditions. Figure 7 depicts subjective ratings of “urges to smoke” over time and by condition.

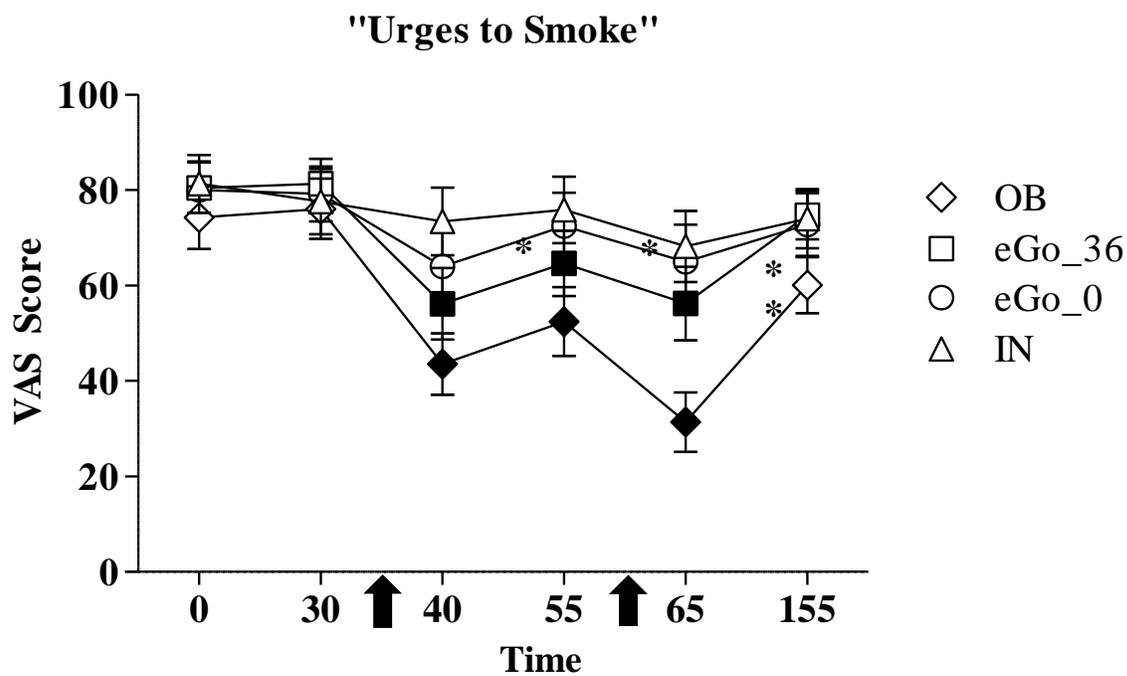


Figure 7. Mean (\pm SEM) for VAS score of “Urges to smoke” from 24 smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline at that time point. Asterisks (*) indicates a significant difference from OB at that time-point for that product.

Hunger. A significant main effect of time [$F(5, 115) = 5.83, p < .01$] was observed for the item “Hunger”. Participants’ mean rating of the item “Hunger” in the OB condition was 23.21 (30.7) at baseline, and was significantly lower than their mean rating of 32.33 (37.0) before the first bout and 33.67 (33.1) following the washout period, [$t_s > 3.44, p_s < .01$]. Participants’ mean rating in the eGo_0 condition was 32.13 (35.4) at baseline, and was significantly lower than their ratings of 47.13 (37.3) following the wash-out period [$t(23) = -2.98, p < .01$]. Similarly, in the IN condition, participants’ mean rating of was 30.88 (33.0) at baseline, significantly lower than their mean rating of 46.96 (33.9) following the wash-out period [$t(23) = -3.02, p < .01$]. Exploratory analyses revealed a significant difference between eGo_36 and the eGo_0 condition following the first bout. Participants in the eGo_36 condition had a mean rating of 20.33 (30.3) that was significantly lower than their mean rating of 37.04 (35.7) in the eGo_0 condition [$t(23) = -2.78, p < .05$].

Tiffany-Drobes Questionnaire of Smoking Urges-Brief. Significant condition by time interactions were observed for Factor 1 (desire and intention to smoke) and Factor 2 (anticipation of relief from smoking abstinence), [$F_s > 4.40, p_s < .01$]. There was a significant main effect of condition observed for Factor 1 [$F(3, 60) = 9.18, p < .001$] and a significant main effect of time observed for Factor 1 and Factor 2 [$F_s > 6.31, p_s < .05$].

Factor 1: Desire and Intention to Smoke. A significant condition by time interaction [$F(12, 240) = 8.71, p < .001$], and main effects of condition [$F(3, 60) = 9.18, p < .001$] and time [$F(4, 80) = 16.90, p < .001$] were observed for Factor 1 (i.e., desire and intention to smoke). Following the first bout, participants’ Factor 1 scores were significantly reduced in the OB condition from a mean baseline score of 34.00 (37.36) to a mean score of 14.63 (24.6) following the first bout, remained lower following the 20- minute rest period (before the second bout) at

22.54 (34.2), and were reduced farther to 12.54 (23.8) following the second bout [$t_s > 3.46, p_s < .01$]. Following the first bout, participants' Factor 1 scores were significantly reduced in the eGo_36 condition from a mean baseline score of 41.50 (40.4) to a mean score of 10.96 (15.3) and then to a mean score of 21.71 (32.3) following the second bout [$t_s > 2.90, p_s < .01$]. Following the first bout, participants' Factor 1 scores were significantly reduced in the eGo_0 condition from a mean baseline score of 29.96 (33.5) to a mean score of 19.9 (26.5), [$t(23) = 2.94, p < .01$].

There were no significant differences in participants' Factor 1 scores between conditions at baseline, although significant differences were also observed across conditions at later time points. Following the first bout, participants' mean Factor 1 score was 13.86 (9.2) in the OB condition, and was significantly lower than the mean score of 20.52 (10.5) in the eGo_0 condition, [$t(23) = -2.46, p < .025$]. Following the second bout, participants' mean Factor 1 score was 8.71 (7.9) in the OB condition, and was significantly lower than the mean score of 17.19 (11.2) in the eGo_36 condition and the mean score of 21.10 (11.1) in the eGo_0 condition [$t_s > -3.69, p_s < .01$]. Following the first bout, participants' mean Factor 1 score was 23.24 (8.7) in the IN condition, and was significantly higher than the mean score of 17.57 (10.9) in the eGo_36, [$t(23) = 2.67, p < .025$]. Following the second bout, participants' mean Factor 1 score was 23.48 (8.8) in the IN condition, and was significantly higher than the mean score of 17.19 (11.2) in the eGo_36, [$t(23) = 3.10, p < .01$]. Exploratory analyses did not reveal any significant differences in participant Factor 1 scores between the eGo_36 and the eGo_0 condition. Figure 8 depicts subjective ratings of desire and intention to smoke over time and by condition.

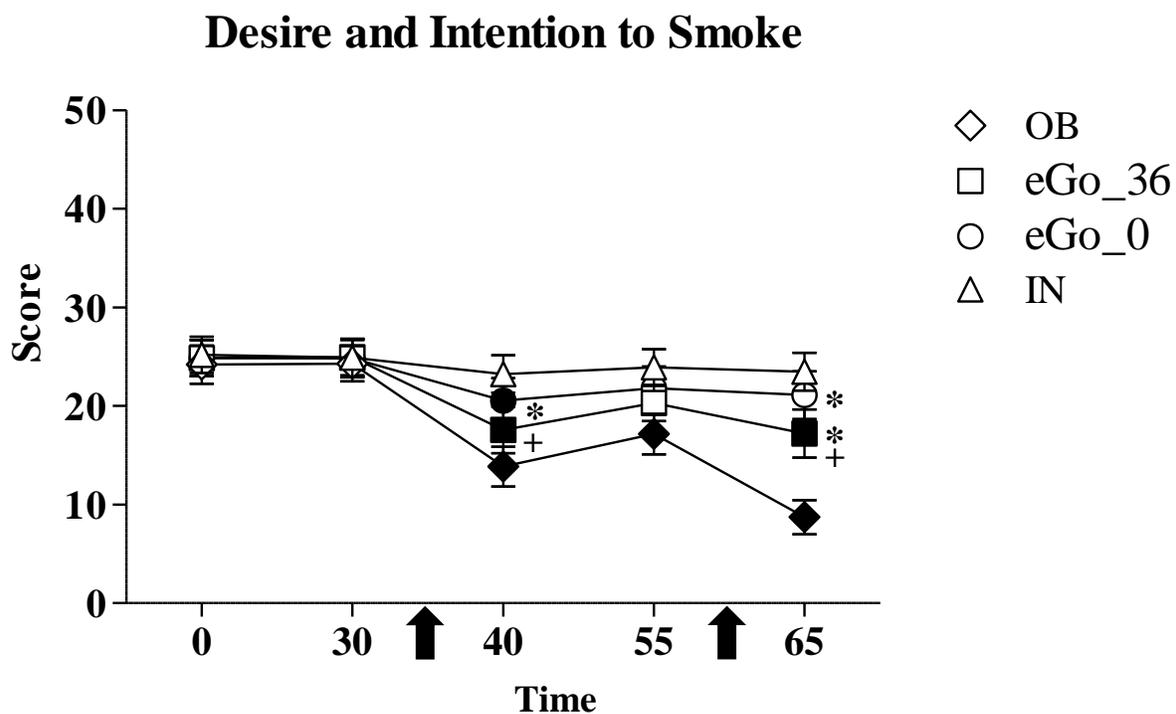


Figure 8. Mean (\pm SEM) for QSU-brief Factor 1 score: Desire and intention to smoke for 21 electronic cigarette naïve smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline at that time point. Asterisks (*) indicates a significant difference from OB and plus sign (+) indicates significant difference from IN indicates significant difference from eGo_36 at that time-point for that product.

Factor 2: Anticipation of Relief from Smoking Abstinence. A significant condition by time interaction was observed for Factor 2 (i.e., anticipation of relief from smoking abstinence) [$F(12, 240) = 4.40, p < .01$], as well as a main effect of time [$F(4, 80) = 6.31, p < .05$]. Following the first bout, participants' Factor 2 scores were significantly reduced in the OB condition from a mean baseline score of 11.24 (8.1) to a mean score of 6.48 (7.4) following the first bout, remained lower following the 20-minute rest period (prior to the second bout) at a mean of 7.71 (8.3), and was reduced farther to 4.71 (5.6) following the second bout [$t_s > 2.80, p_s < .025$]. There were no significant differences in participants' Factor 2 score between conditions at baseline, although significant differences were also observed across conditions at later time points. Following the second bout, participants' mean Factor 2 score was 4.71 (5.6) in the OB condition, and was significantly lower than the mean score of 8.48 (7.9) in the eGo_0 condition, [$t(23) = -2.72, p < .025$]. Exploratory analyses did not reveal any significant differences between the eGo_36 and eGo_0 conditions.

Direct Effects of Nicotine Scale. A significant condition by time interaction [$F(12, 240) = 2.61, p < .05$] and main effects of condition [$F(3, 60) = 5.62, p < .01$] and time [$F(4, 80) = 5.14, p < .01$] were observed for the item "Light-headed". No other significant interactions or items were observed for the Direct Effects of Nicotine Scale items.

Light-headed. Participant ratings of "Light-headed" significantly increased in the OB condition from 8.29 (16.3) at baseline to 38.62 (38.0) after the first bout [$t(23) = -4.35, p < .001$]. No other significant changes from baseline were observed within conditions.

There were no significant differences in participants' ratings of the item "Light-headed" between conditions at baseline, although significant differences were also observed across conditions at later time points. Following the first bout, participants' ratings of the item "Light-

headed” was 38.62 (38.02.) in the OB condition, and was significantly higher than their mean rating of 17.52 (27.2) in the eGo_36 condition and their mean rating of 12.86 (19.9), in the eGo_0 condition [$t_s > 2.49, p_s < .025$]. Following the 20-minute rest period (prior to the second bout), participants’ mean rating in the OB condition was 17.43 (26.3), and was significantly higher than participants’ mean ratings of 7.95 (15.0) in the eGo_0 condition [$t(23) = 2.76, p < .025$]. Following the second bout, participants’ mean in the OB condition rating was 18.29 (21.5), and was significantly higher than participants’ mean rating of 7.71 (14.7) in the eGo_0 condition [$t(23) = 3.04, p < .01$]. Exploratory analyses did not reveal any significant differences between the eGo_36 and eGo_0 conditions. Figure 9 depicts subjective ratings of light-headedness over time and by condition.

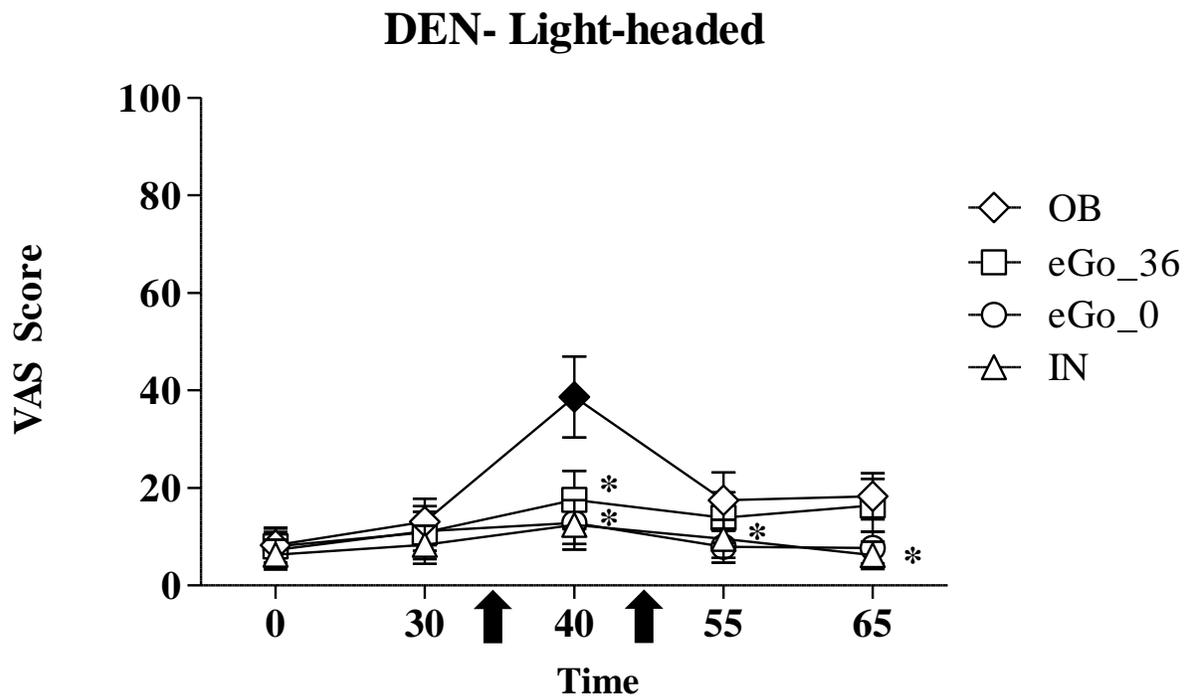


Figure 9. Mean (\pm SEM) for VAS score of the item “light-headed” from 21 electronic cigarette naïve smokers. Arrows represent the onset of each 10-puff directed product use bout (30-seconds between each puff). Filled symbols indicate a significant difference from baseline at that time point. Asterisks (*) indicates a significant difference from OB, plus sign (+) indicates significant difference from IN, and (#) pound symbol indicates significant difference from eGo_36 at that time-point for that product.

Direct Effects of Product Scale. A significant condition by time interaction was observed for the item “Did the product calm you down?” [$F(6, 126) = 2.26, p < .05$]. Significant main effects of condition were observed for the items “Did the product make you feel more awake?”, “Did the product calm you down?”, “Did the product help you concentrate?”, “Did the product make you dizzy?”, “Was the product pleasant?”, “Did the product reduce your hunger for food?”, “Would you like to use another product right now?”, “Was the product satisfying?”, and “Did the product taste good?” [$F_s > 8.16, p_s < .001$]. Significant main effects of time were observed for the items “Did the product make you feel more awake?”, “Did the product calm you down?”, “Was the product pleasant?”, and “Would you like to use another product right now?” [$F_s > 4.59, p_s < .05$].

Calm. A significant condition by time by abstinence status interaction was observed for the item “Did the product calm you down?” [$F(6, 120) = 2.51, p < .05$]. However, post-hoc independent t-tests did not reveal any significant differences between participants that were abstinent and those who were not abstinent at any time point in any condition. Separate analyses for abstinent and non-abstinent participants revealed that abstinent participants did not have a significant interaction [$F(6, 72) = 1.11, p > .05$] but the non-abstinent participants did have a significant interaction [$F(6, 48) = 3.73, p < .01$]. However, a similar main effect of condition was observed for abstinent participants [$F(3, 36) = 6.09, p < .01$] and for non-abstinent participants [$F(3, 24) = 10.19, p < .001$] and a similar main effect of time was observed for abstinent participants [$F(2, 24) = 5.53, p < .05$] and non-abstinent participants [$F(2, 16) = 5.97, p < .05$]. Therefore, because the overall pattern of results was similar and there were no significant differences found in the post hoc analyses, the data were collapsed across abstinence status and all participant data were analyzed together.

When collapsed across abstinence status, results revealed a significant condition by time interaction [$F(6, 126) = 2.26, p < .05$], main effect of condition [$F(3, 63) = 14.86, p < .001$], and a main effect of time [$F(2, 42) = 11.43, p < .01$]. Significant differences across conditions were observed. Following the first bout, participants had a greater mean rating of 70.55 (29.2) in the OB condition than the mean rating of 40.09 (35.9) in the eGo_36 condition and the mean rating of 32.45 (33.0) in the eGo_0 condition [$t_s > 3.47, p_s < .01$]. Following the 20-minute rest period (prior to the second bout), participants had a significantly higher mean rating of 57.68 (35.0) in the OB condition than their mean rating of 35.05 (35.8) in the eGo_36 condition and their mean rating of 30.09 (32.1) in the eGo_0 condition [$t_s > 2.85, p_s < .025$]. Following the second bout, participants had a significantly greater mean rating of 47.82 (35.2) in the OB condition than their mean rating of 28.23 (29.6) in the eGo_36 condition [$t(23) = 2.97, p < .01$]. Comparisons to inhaler revealed that following the first bout, participants had a significantly lower mean rating of 18.50 (20.7) in the IN condition than their mean rating of 40.09 (35.9) in the eGo_36 condition [$t(23) = 2.60, p < .025$]. Following the 20-minute rest period (prior to the second bout), participants had a significantly lower mean rating of 13.14 (19.4) in the IN condition than their mean rating of 35.05 (35.8) in the eGo_36 condition [$t(23) = 2.78, p < .025$]. Exploratory analyses did not reveal any significant differences between the eGo_36 condition and the eGo_0 condition.

Awake. Significant main effects of condition [$F(3, 63) = 15.45, p < .001$] and time [$F(2, 42) = 6.71, p < .01$] were observed for the item “Did the product make you feel more awake?”. Collapsed across time, participants had a significantly greater mean rating of 55.33 (30.7) in the OB condition compared to their mean rating of 32.36 (31.4) in the eGo_36 condition, and their mean rating of 27.35 (30.5) in the eGo_0 condition, [$t_s > 3.73, p_s < .01$]. Collapsed across time,

participants had a significantly lower mean rating of 11.03 (18.4) in the IN condition compared to their mean rating of 32.36 (31.4) in the eGo_36 condition, [$t(23) = -3.11, p < .01$].

Exploratory analyses did not reveal any significant differences between the eGo_36 condition and the eGo_0 condition.

Concentrate. A significant main effect of condition [$F(3, 63) = 11.49, p < .001$] was observed for the item “Did the product help you concentrate?”. Collapsed across condition, participants had a higher mean rating of 45.38 (34.87) in the OB condition compared to their mean rating of 22.83 (30.3) in the eGo_36 condition, and their mean rating of 22.32 (31.1) in the eGo_0 condition [$ts > 3.19, ps < .01$]. Collapsed across condition, participants had a lower mean rating of 8.42 (15.4) in the IN condition compared to the mean rating of 22.83 (30.3) in the eGo_36 condition [$t(23) = -2.56, p < .025$]. Exploratory analyses did not reveal any significant differences between the eGo_36 condition and the eGo_0 condition.

Dizzy. A significant time by abstinence status interaction was observed for the item “Did the product make you dizzy” [$F(2, 40) = 4.58, p < .05$]. Separate analyses for abstinent and non-abstinent participants revealed that abstinent participants did not have a significant interaction [$F(6, 72) = 0.68, p > .05$] but the non-abstinent participants did have a significant interaction [$F(6, 48) = 4.07, p < .05$]. Although a similar main effect of condition was observed for abstinent participants [$F(3, 36) = 5.39, p < .01$] and for non-abstinent participants [$F(3, 24) = 3.75, p < .05$] participants, separate analyses revealed different effects of time. Abstinent participants did not have a significant effect of time [$F(2, 24) = 0.07, p > .05$] while non-abstinent participants did have a significant effect of time [$F(2, 16) = 9.21, p < .01$]. However, post-hoc independent t-tests did not reveal any significant differences between participants that were abstinent and those

who were not abstinent at any time point. Therefore, participants were collapsed across abstinence status and data were analyzed together.

Collapsed across abstinence status, a significant main effect of condition [$F(3, 63) = 8.16, p < .001$] was observed. Post hoc analyses revealed that collapsed across time, participants had a significantly higher mean rating of 34.41 (28.2) in the OB condition compared to their mean rating of 18.76 (23.9) in the eGo_36 condition and their mean rating of 12.59 (19.8) in the eGo_0 condition, [$ts > 2.71, ps < .05$]. Exploratory analyses revealed a significant difference between the eGo_36 and the eGo_0 condition following the first bout. Participants' had a mean rating of 24.14 (27.9) in the eGo_36 condition that was significantly higher than their ratings of 10.50 (17.5) in the eGo_0 condition [$t(21) = 3.27, p < .01$].

Pleasant. Significant main effects of condition [$F(3, 63) = 34.26, p < .001$] and time [$F(2, 42) = 4.59, p < .05$] were observed for the item "Was the product pleasant?". Collapsed across time, participants had a mean rating of 85.17 (16.7) in the OB condition that was significantly higher than their mean rating of 42.29 (35.9) in the eGo_36 condition and their mean rating of 50.80 (33.2) in the eGo_0 condition [$ts > 5.44, ps < .001$]. Collapsed across time, participants had a significantly lower mean rating of 12.62 (17.4) in the IN condition than their mean rating of 42.29 (35.9) in the eGo_36 condition and their mean rating of 50.80 (33.2) in the eGo_0 condition [$ts > 3.39, ps < .001$]. Exploratory analyses revealed a significant difference between the eGo_36 condition and the eGo_0 condition following the first bout. Participants' had a mean rating of 41.18 (35.5) in the eGo_36 condition that was significantly lower than their ratings of 56.09 (35.6) in the eGo_0 condition [$t(21) = 2.20, p < .01$]. Figure 10 depicts mean subjective ratings for the item "Was the product pleasant?" by condition.

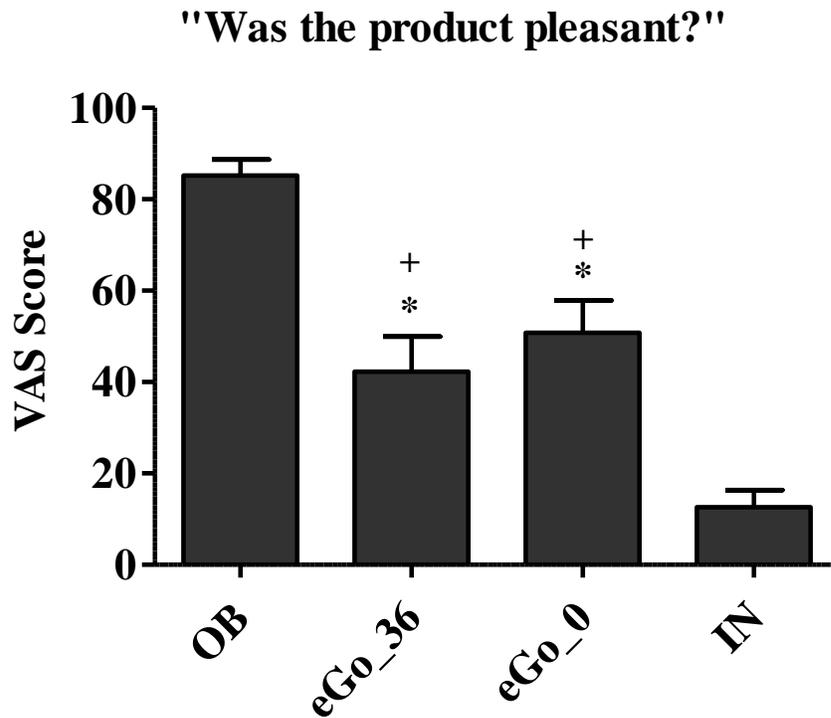


Figure 10. Mean ratings of “was the product pleasant?” (+ SEM) for 22 electronic cigarette naïve smokers after use of products. Asterisk (*) indicates a significant difference from OB and plus sign (+) indicates significant differences from IN (*t*-test, *ps* <.05).

Reduced Hunger. A significant main effect of condition [$F(3, 63) = 9.54, p < .001$] was observed for the item “Did the product reduce your hunger for food?” Collapsed across time, participants had a significantly higher mean rating of 36.62 (21.0) in the OB condition compared to their mean rating of 18.83 (25.0) in the eGo_36 condition and their mean rating of 16.27 (20.7) in the eGo_0 [$ts > 3.67, ps < .01$]. Exploratory analyses did not reveal any significant differences between the eGo_36 condition and the eGo_0 condition.

Right Now. A significant main effect of time [$F(2, 42) = 5.70, p < .01$] was observed for the item “Would you like to use another product right now?” Collapsed across condition, participants had a significantly lower mean rating of 33.31 (23.0) following the second bout, compared to their mean rating following the first bout of 43.43 (24.2) and their mean rating prior to the second bout of 42.63 (25.0) [$ts > 2.63, ps < .05$]. Exploratory analyses did not reveal any significant differences between the eGo_36 condition and the eGo_0 condition.

Satisfy. A significant main effect of condition [$F(3, 63) = 44.20, p < .001$] was observed for the item “Was the product satisfying?”. Collapsed across time, participants’ mean rating in the OB condition was 84.91 (16.9), and was significantly higher than their mean rating of 41.77 (34.2) in the eGo_36 condition and their mean rating of 44.82 (28.6) in the eGo_0 condition [$ts > 3.68, ps < .001$]. Collapsed across time, participants’ mean rating in the IN condition was 12.03 (19.0), significantly lower than their mean rating of 41.77 (34.2) in the eGo_36 condition and their mean rating of 44.82 (28.6) in the eGo_0 condition [$ts > 3.92, ps < .01$]. Exploratory analyses did not reveal any significant differences between the eGo_36 condition and the eGo_0 condition. Figure 11 depicts participants’ mean subjective ratings of the item “Was the product satisfying?” by condition.

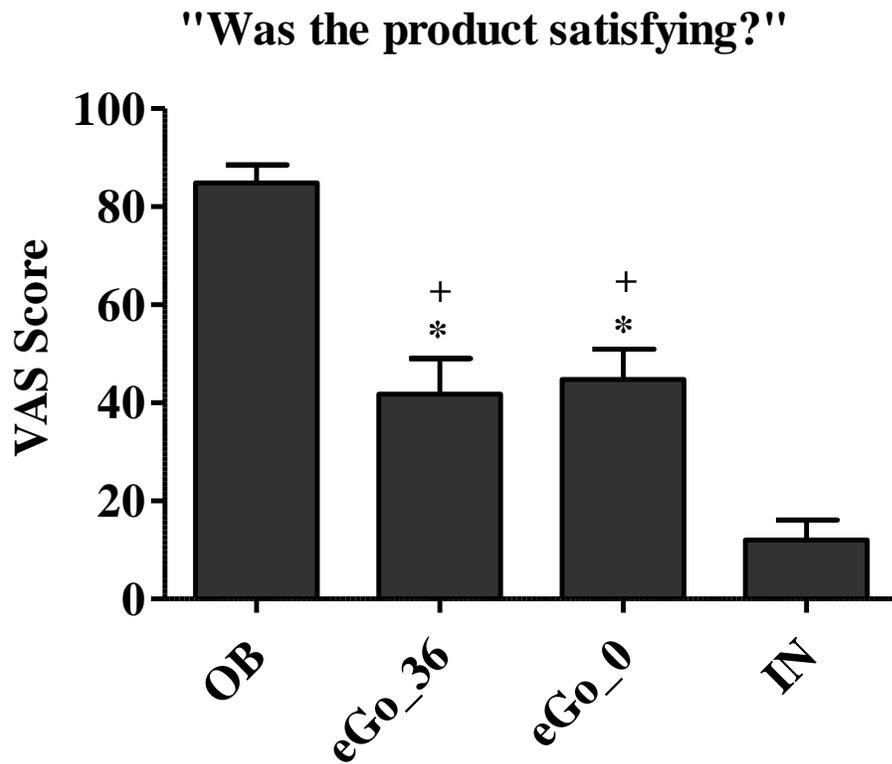


Figure 11. Mean ratings of “was the product satisfying?” (+ SEM) for 22 electronic cigarette naïve smokers after use of products. Asterisk (*) indicates a significant difference from OB and plus sign (+) indicates significant differences from IN (*t*-test, *ps* <.05).

Taste Good. A significant time by abstinence status interaction was observed for the item “Did the product taste good” [$F(2, 40) = 9.66, p < .001$]. Separate analyses for abstinent and non-abstinent participants revealed that abstinent participants had a similar, non-significant interaction [$F(6, 72) = 1.20, p > .05$] as non-abstinent participants [$F(6, 48) = 1.74, p > .05$]. Results revealed a similar main effect of condition for abstinent participants [$F(3, 36) = 34.66, p < .001$] and for non-abstinent participants [$F(3, 24) = 11.68, p < .001$]. However, separate analyses revealed different effects of time for abstinent participants [$F(2, 24) = 0.04, p > .05$] than for non-abstinent participants [$F(2, 16) = 15.03, p < .01$]. Post hoc tests revealed that there was a significant difference between participants who abstained and participants who did not abstain in the eGo_0 condition following the rest period and after the second product bouts. More specifically, participants who abstained had a mean rating of 48.5 (32.1) following the 20-minute rest period compared to participants who did not abstain mean rating of 26.00 (29.7), [$t(20) = 2.93, p < .01$]. Similar results were observed following the second bout, such that participant who abstained had a higher mean rating of 57.92 (31.1) compared to the non-abstinent participants mean of 36.78 (33.8), [$t(20) = 2.31, p < .05$]. Because similar interactions and main effects were revealed when the two groups were analyzed separately the final post-hoc analyses were conducted collapsed across abstinence status.

Significant main effects of condition [$F(3, 63) = 40.48, p < .001$] and time [$F(2, 42) = 3.85, p < .05$] were observed for the item “Did the product taste good?”. Collapsed across time, participants had a mean rating in the OB condition of 83.45 (17.3), and it was significantly higher than their mean rating of 41.61 (32.9) in the eGo_36 condition and their mean rating of 51.18 (31.1) in the eGo_0 condition [$t_s > 5.48, p_s < .001$]. Collapsed across time, participants had a mean rating in the IN condition of 7.68 (13.1), significantly lower than their mean rating of

41.61 (32.9) in the eGo_36 condition and their mean rating of 51.18 (31.1) in the eGo_0 condition [$ts > 4.30$, $ps < .001$]. Exploratory analyses revealed a significant difference between the eGo_36 condition and the eGo_0 condition following the first bout. Participants' had a mean rating of 40.55 (34.3) in the eGo_36 condition that was significantly lower than their ratings of 58.14 (31.3) in the eGo_0 condition [$t(21) = 2.20$, $p < .05$]. Figure 12 depicts participants' mean subjective ratings of the item "Did the product taste good?" by condition.



Figure 12. Mean ratings of “did the product taste good?” (+ SEM) for 22 electronic cigarette naïve smokers after use of products. Asterisk (*) indicates a significant difference from OB and plus sign (+) indicates significant differences from IN (t -test, $ps < .05$).

Additional Exploratory Analyses

Exploratory correlations were conducted on the mean MCP crossover points, the FTND total score, and the number of cigarettes participants reported smoking each day at screening to examine if indicators of nicotine dependence was at all related to participants' choices on the MCP. A significant correlation was observed between the FTND total score and the mean MCP crossover point for the OB condition ($r = .41, p < .05$). Additional significant correlations were observed for the number of cigarettes participants reported smoking each day at screening and the mean crossover point in the eGo_0 condition ($r = .58, p < .01$) and the mean crossover point in the OB condition ($r = .51, p < .05$). No other correlations were observed between mean MCP crossover points and indicators of dependence.

Additional exploratory analyses were conducted to examine if there was a difference in participants' mean MCP crossover points and ratings of "Did the product taste good?" between participants who used tobacco flavor liquid ($n = 7$) and participants that used menthol flavor liquid ($n = 17$). Independent t-tests did not reveal any significant differences between the traditional tobacco flavor and the menthol flavor on mean MCP crossover points or the subjective item "Did the product taste good?".

Discussion

Overview

Electronic cigarettes have become popular tobacco products (Persokie, Donaldson, & King, 2016; Schoenborn & Gindi, 2015) that are capable of delivering cigarette-like doses of nicotine to users (Hiler et al., 2017; Wagener et al., 2017). Electronic cigarettes have been advertised as reduced harm products and cessation aids (Pearson, Richardson, Niaura, Vallone, & Abrams, 2012), and not surprisingly, the majority of electronic cigarette users are current

(15.9%) or past (22.0%) cigarette smokers (Schoenborn & Gindi, 2015). Many individuals (i.e., young adults, electronic cigarette users, smokers) perceive electronic cigarettes to be less harmful and/or safer than combustible cigarettes (Adkison et al., 2013; Choi & Forester, 2013; Choi, Fabian, Mottey, Corbett, & Forster, 2012; Dockrell, Morison, Bauld, & McNeill, 2013; Etter & Bullen, 2011; Pearson, Richardson, Niaura, Vallone, & Abrams, 2012; Shi, Cummings, & Zhu, 2016). However, much of the electronic cigarette toxicity research suggests that these products are not harm free (Costigan & Meredith, 2015; Jensen, Luo, Pankow, Strongin, & Peyton, 2015; Kosmider et al., 2014; Tayyarah & Long, 2014; Tierney, Karpinski, Brown, Luo, & Pankow, 2016; Varlet, Farsalinos, Augsburger, Thomas, & Etter, 2015; Walley & Jenssen, 2015). For this reason, concerns have been raised about the impact of electronic cigarette on public health and much debate has followed. The FDA extended the definition of tobacco products to include electronic cigarettes (81 FR 28973, 2016) and will move forward with creating electronic cigarette regulations. While much research is still needed to understand the full impact that electronic cigarettes pose on public health, this study aimed to compare the abuse liability of an electronic cigarette with and without nicotine (eGo_36 and eGo_0) to 1) traditional cigarettes (OB) and 2) to an FDA approved nicotine inhaler (IN). A total of 24 traditional cigarette smokers participated in four, ~ 4.5-hour, Latin-square ordered sessions in which abuse liability was assessed via the multiple-choice procedure (MCP), blood nicotine delivery, and subjective effects (i.e., nicotine abstinence suppression and direct effects of product and nicotine).

For the MCP, it was hypothesized that the eGo_36 and the eGo_0 would have lower crossover points, and thus less reinforcing efficacy than OB, however this was only true for eGo_36; eGo_0 did not differ significantly from OB. The second hypothesis was that the

eGo_36 would have a higher MCP crossover point than the eGo_0, but there was no significant difference between eGo_0 and eGo_36 on the MCP. In addition, eGo_36 and eGo_0 had significantly higher mean crossover points on the MCP than IN, suggesting that they were more reinforcing than IN. The third hypothesis was that OB would deliver more nicotine than eGo_0 and eGo_36. Results indicated that OB delivered significantly more nicotine than eGo_0, but did not differ significantly from the amount of nicotine delivered by eGo_36. The eGo_36 delivered significantly more nicotine than IN and eGo_0. The final hypothesis that OB would reduce nicotine abstinence symptoms more than eGo_0 and eGo_36 was found to be true for multiple items of nicotine abstinence suppression. However, eGo_36 and eGo_0 did reduce nicotine abstinence symptoms to a greater degree than IN.

Multiple-Choice Procedure

The mean MCP crossover point in the OB condition was \$1.42, significantly higher than the mean crossover point in the eGo_36 condition that was \$0.87. This finding is similar to previous studies that have found that some nicotine-containing electronic cigarettes have a lower reinforcing efficacy compared to traditional cigarettes when using the MCP (McPherson et al., 2016; Vansickel, Weaver, & Eissenberg, 2012). However, one study that also investigated electronic cigarette abuse liability using the MCP found that not all electronic cigarettes had lower crossover values than traditional cigarettes (Barnes, Bono, Lester, Eissenberg, & Cobb, 2017). This study examined the impact of flavor and harm messaging using the MCP. In this study, participants' MCP crossover point for the tobacco flavored electronic cigarette (containing 36 mg/ml nicotine) did not differ significantly from participants' own brand of cigarette, although significant differences were observed between the unflavored, menthol, and cherry flavored electronic cigarettes (also containing 36 mg/ml nicotine) and participants' own brand of

cigarettes (Barnes, Bono, Lester, Eissenberg, & Cobb, 2017). Also, in the current study, the OB crossover point of \$1.42 and the eGo_0 crossover point of \$0.96 did not differ significantly. Furthermore, the mean eGo_36 crossover point of \$0.87 and the mean eGo_0 MCP crossover point of \$0.96 were higher than the mean IN crossover point of \$0.32, indicating that this particular electronic cigarette has a higher reinforcing efficacy than the IN.

Nicotine Delivery and Physiological Effects

Following the first and second product bout there was a significant increase in blood nicotine level for the OB and eGo_36 conditions, but no significant differences between these two conditions. Neither the eGo_0, nor the IN condition, had significant increases in blood nicotine concentration after the first or second bout. More specifically, a mean blood nicotine concentration of 13.64 ng/ml was observed following the first OB product bout (increase from baseline = 10.09 ng/ml), and a mean blood nicotine concentration of 14.87 ng/ml was observed following the second OB product bout, (increase from baseline = 11.31 ng/ml). These means are somewhat lower than results reported from previous studies examining nicotine delivery of tobacco cigarettes (post-product use mean raw concentration of 24.4 ng/ml, Lopez et al., 2016b; post-product use mean raw concentration of 18.8 ng/ml, Vansickel et al., 2010).

Significant increases in blood nicotine were observed after eGo_36 use. While on average these increases in blood nicotine concentration were lower than OB, blood nicotine levels did not significantly differ from OB throughout the session. For the eGo_36, a mean blood nicotine concentration of 8.51 ng/ml was observed following the first eGo_36 product bout, (mean increase from baseline = 5.35 ng/ml). A mean blood nicotine concentration of 11.29 ng/ml was observed following the second eGo_36 product bout, (mean increase from baseline = 8.13 ng/ml). Similar results have been found in previous studies examining the nicotine delivery of a

similar electronic cigarette in current cigarette smokers (post-product use mean raw concentration of 9.5 ng/ml, Lopez et al., 2016b; mean increase from baseline of 6.9 ng/ml, Hiler et al., 2017).

Furthermore, nicotine was physiologically active in the OB condition, as indicated by elevations in heart rate and blood pressure. In this condition, participants' heart rate increased from a baseline of 67.08 bpm to 79.16 bpm during the first bout and increased to 77.73 bpm during the second bout. Participants' diastolic blood pressure increased from a baseline of 73.15 mmHg to 82.44 mmHg during the first bout in the OB condition. Additionally, nicotine was physiologically active in the eGo_36 condition, as indicated by elevations in heart rate. In this condition, participants' heart rate increased from a baseline of 67.54 bpm to 72.59 bpm during the first bout and to 71.37 bpm during the second bout. These results are similar to previous studies that have found electronic cigarettes with nicotine to increase heart rate and blood pressure (Lopez et al., 2016b; Hiler et al., 2017).

Subjective effects

Nicotine Abstinence Suppression. The greatest reductions in nicotine abstinence symptoms were seen after OB product use. Following the first and second OB bout, participants had significant reductions in cigarette cravings, urges to smoke, intentions to smoke, and anticipation of relief from abstinence symptoms. However, eGo_36 was also able to significantly reduce cigarette cravings, urges to smoke, and intentions to smoke. These results are similar to previous studies that have found that nicotine containing electronic cigarettes are capable of reducing nicotine abstinence symptoms in cigarette smokers (Hiler et al., 2017; Lopez et al., 2016b; Vansickel, Cobb, Weaver & Eissenberg, 2010; Vansickel & Eissenberg, 2013). Interestingly, the eGo_0 was found to significantly suppress intentions to smoke following the

first bout. A previous study demonstrated that participants' expectation of nicotine from a non-nicotine containing electronic cigarette was capable of suppressing nicotine abstinence symptoms (Copp et al., 2015); however, other studies have found that electronic cigarettes without nicotine do not substantially reduce nicotine abstinence symptoms in smokers (Hiler et al., 2017). IN did not reduce nicotine abstinence symptoms significantly.

When comparing products to each other, OB reduced cigarette cravings, urges to smoke, and intentions to smoke significantly more than the eGo_36. Moreover, OB reduced cigarette cravings, urges to smoke, intentions to smoke, and anticipation of relief from abstinence symptoms significantly more than eGo_0. These findings are consistent with previous literature that found greater reductions in nicotine abstinence symptoms in smokers following OB consumption compared to electronic cigarette consumption (Lopez et al., 2016b; Vansickel, Weaver, & Eissenberg, 2012). Finally, eGo_36 reduced cigarette cravings and intentions to smoke significantly more than IN, suggesting that eGo_36 is more negatively reinforcing than IN.

Subjective Reinforcing Effects.

The greatest increases in subjective reinforcement were seen after OB product use. OB was rated as more calming, pleasant, satisfying, and better tasting compared to eGo_36 and eGo_0, suggesting that OB is significantly more reinforcing than eGo_36 and eGo_0. Furthermore, participants had higher ratings of feeling awake, dizzy, and light-headed in the OB condition than in the eGo_36 and the eGo_0 conditions. These results are similar to previous results that have shown that electronic cigarettes with nicotine produce lower levels of subjective reinforcement than OB (Lopez et al., 2016b; McPherson et al., 2016; Vansickel, Weaver, & Eissenberg, 2012).

However, both eGo_36 and eGo_0 were found to be more pleasant, satisfying, and better tasting than IN. Furthermore, in the eGo_36 condition, participants felt more awake and calm than in the IN condition. These results suggest that both nicotine and non-nicotine containing electronic cigarettes are more reinforcing than IN, which suggest an elevated abuse liability. Finally, eGo_0 was rated as more pleasant and better tasting than eGo_36. Electronic cigarette users reported that electronic cigarette liquids with higher nicotine concentrations tend to have a stronger throat hit (Etter 2016), therefore the current result may indicate that the 36 mg/ml nicotine concentration was too harsh for some users.

Summary of Results and Alternative Explanations of Findings

Overall, this study was similar to previous studies suggesting that electronic cigarettes have a lower abuse potential than traditional cigarettes. However, because the electronic cigarette used in this study was capable of delivering nicotine to users at levels similar to traditional cigarettes (i.e., the 36 mg/ml condition), and because both the electronic cigarettes were subjectively more reinforcing and reduced nicotine abstinence symptoms to a greater degree than that of a traditional form of NRT (nicotine inhaler), caution is warranted for the use of these products in certain populations. Specifically, precautions should be taken to prevent nicotine-naïve individuals and youth from using these products, as repeated use of these products could lead to dependence. The eGo_36 was capable of reducing nicotine abstinence symptoms in the current cigarette smoking sample which had moderate levels of nicotine dependence (FTND score mean = 5.2). These results suggest that the eGo_36 may have utility for nicotine dependent smokers who have difficulty quitting using traditional means. Interestingly, eGo_0 did not significantly differ from traditional cigarettes on the MCP and was found to be more subjectively

reinforcing than the IN; these findings warrant further investigations as they suggest that electronic cigarette abuse liability extends beyond factors related to nicotine delivery.

While this study had similar results to previous studies that demonstrated that electronic cigarettes have a lower abuse liability than traditional cigarettes, some of the current studies results, interpreted together, may explain a few of the more surprising findings. For example, participants had significantly lower ratings of “craving a cigarette/nicotine” in the OB condition than in the eGo_0 and the eGo_36 condition following the washout period, this may indicate that the 1.5 hour washout period was not sufficient to create equivalent levels of abstinence symptoms across conditions at this time point. This difference may have affected participants’ choices on the MCP, such that having fewer symptoms of nicotine abstinence may have led participants in the OB condition to choose money over puffs at greater rates than they would if they were in a similar state of abstinence (as in the other conditions). Therefore, differences in nicotine abstinence symptoms across conditions before the MCP may have falsely lowered the reinforcing efficacy (i.e., crossover point) of OB, thus, may be why the current study did not find a significant difference between eGo_0 and OB. In previous studies using the MCP, participants’ sampled the products on a separate day as the experimental sessions to provide participants’ with experience with the products while also limiting their exposure to products before the MCP to ensure a state of abstinence. Having participants sample the products on a separate day and come into the laboratory 12 hours abstinent before MCP administration would have likely resulted in greater tendency to choose product over money, specifically OB, as participants would have likely been in a greater state of abstinence than they were in the current study when the MCP followed two, 10-puff directed bouts 1.5 hours prior to the MCP. While this is speculative, on average (but not significantly different), OB had a higher crossover point

than eGo_0 and eGo_36, and subjective measures indicative of abuse liability also suggest that OB has a higher abuse liability than eGo_0 and eGo_36 in cigarette smokers. However, these results may also represent a possible novelty effect, as the sample was electronic cigarette naïve (< 20 lifetime uses). More specifically, MCP values for eGo_36 and eGo_0 might be higher in this study than in a real-world setting because the products were new and possibly more interesting to participants. Over time, participants may not value these products as highly, once novelty has worn off.

Additionally, differences in participants' MCP crossover point could have been influenced by the harshness of high nicotine concentration in the eGo_36 condition, as higher nicotine concentrations have been reported to provide a stronger throat hit (Etter, 2016). The eGo_36 may have had a harsh throat hit and may have been aversive to use. As a result, participants may have been less willing to use the product again. This may have led to the similar reinforcing efficacy of the eGo_36 and eGo_0 on the MCP, despite the eGo_36 reducing nicotine abstinence symptoms to a significantly greater degree than the eGo_0. Future research would benefit greatly from exploring factors beyond nicotine delivery that affect electronic cigarette abuse liability, such as flavors and sensory cues.

Regulatory Implications

The FDA gained authority to regulate electronic cigarettes in August 2016 (81 FR 28973, 2016). In order to develop policies and regulations for electronic cigarettes that maximize public health and minimize public harm, the FDA requires a great deal of research in order to conduct cost/benefit evaluations. Clinical laboratory studies, like the current study, are useful in estimating the population level health impacts of electronic cigarettes and can also be used to test potential regulations before they are made rules. Specifically, this study can help policy makers

develop the appropriate regulations for these new products that are proportionate to current or future regulations of tobacco and nicotine products with established high and low abuse liabilities.

The results from this study suggest that caution should be taken in the marketing and availability of these products in places that youth come into contact with, as these products may have an elevated abuse potential compared to the nicotine inhaler and are not risk free to use. Policies that limit the sale of these products in stores that are near schools or stores that youth and adolescents frequent should be considered. Furthermore, warning labels should include risk of addiction as these products are capable of delivering significant amounts of nicotine to users. In addition, electronic cigarette devices and liquids should have child proof packaging and safety features in order to reduce accidental exposure to nicotine.

The results from this study also suggest that these products are able to suppress nicotine abstinence symptoms to a greater degree than the nicotine inhaler, and therefore, may have utility for smokers who have been unsuccessful in quitting smoking through traditional means. However, the current study only measured acute nicotine abstinence suppression; future research is needed to understand the efficacy of these products to suppress nicotine abstinence symptoms over longer periods of abstinence and to find optimal devices and liquids for smokers looking to switch completely from cigarettes. In addition, further research is needed in order to understand how additional electronic cigarette features such as flavor, sensory cues, device settings, etc. affect the abuse liability of these products. Finally, these studies should be conducted in a variety of populations in order to understand fully the impact that these products pose to population health.

Limitations

The current study has several limitations. The first limitation is that not all participants abstained; specifically, 42% of the sample had baseline blood nicotine concentrations greater than the 5.0 ng/ml cutoff. When data were analyzed to examine the effect of abstinence status on the outcome measures, only a few subjective items were significant (i.e., “Craving a cigarette/nicotine”, “Urges to smoke”, “Calm”, “Dizzy”, and “Taste good”), and most post-hoc tests did not reveal any significant differences between abstinent and non-abstinent groups, likely because this study was not powered to detect between subjects effects of abstinence status. Future studies would benefit from including a 1-hour waiting period prior to the start of the session in order to assure that all participants are abstinent for at least 1 hour, as in Spindle et al., (in press).

Another limitation of this study is that it only examined OB flavor matched electronic cigarette liquids (i.e., tobacco and menthol) and only at two nicotine concentrations (i.e., 0 mg/ml and 36 mg/ml). Future studies would benefit from examining different flavors and a wider variety of nicotine concentrations, among other variables, to better understand factors that impact electronic cigarettes’ abuse liability. Furthermore, this study used a low-powered, pen-style electronic cigarette. As more advanced styles of electronic cigarettes (i.e., variable-voltage devices) become more popular, future research would benefit from examining the abuse liability of more advanced style electronic cigarettes, and to determine how device power affects their abuse liability profile. Higher-powered devices have been found to deliver cigarette-like doses of nicotine to users (Wagener et al., 2017), and thus more advanced models of electronic cigarettes may have a higher abuse liability.

Another limitation of this study is that there were no measures of participants' sensory experience while using these products (i.e., throat hit, harshness, visibility of aerosol/smoke). This study would have also benefited from providing participants with more monetary choices that had smaller intervals between the choices to allow for more precise measurement of the reinforcing efficacy of the products measured in the current study. Despite these limitations, this study provides a unique understanding of the abuse liability of an electronic cigarette containing 0 mg/ml and 36 mg/ml nicotine liquid.

Conclusions

The results suggest that the electronic cigarette and the liquids examined in this study have a moderate level of abuse liability in cigarette smokers. Overall, traditional cigarettes have a higher abuse liability than the electronic cigarette and liquids investigated in the current study. Specifically, the electronic cigarette (with 36 mg/ml nicotine and 0 mg/ml nicotine) examined in this study was found to have higher abuse liability than the nicotine inhaler. The electronic cigarette containing 36 mg/ml nicotine concentration liquid reduced nicotine abstinence symptoms to a greater degree than the 0 mg/ml nicotine containing electronic cigarette. However, the abuse liability profiles of the 0 mg/ml and the 36 mg/ml nicotine liquid containing electronic cigarettes were similar in terms of MCP crossover point and subjective reinforcing effects, suggesting that factors beyond nicotine delivery likely influence the abuse liability of electronic cigarettes.

Results from this study demonstrate that a 36 mg/ml nicotine electronic cigarette is capable of suppressing nicotine abstinence symptoms in dependent cigarette smokers, and therefore may indicate that electronic cigarettes have acute utility as a cigarette alternative product. More research is needed to determine long-term efficacy of these products as a

cessation aid. However, the results from this study indicate that both the electronic cigarettes had a higher reinforcing efficacy than the nicotine inhaler. This elevated abuse liability may be contributing to the growing popularity of electronic cigarettes. Therefore, precautions should be taken to prevent the initiation and use of these products in vulnerable populations such as nicotine-naïve individuals and youth. Future electronic cigarette regulations would benefit from limiting the access and marketing of these products to youth and young adults as the use of these products has been shown to be a risk factor for the uptake of traditional cigarettes (Leventhal et al., 2015; Soneji et al., 2017; Watkins et al., 2018). Regulators may want to consider regulations that limit access and the availability of electronic cigarette devices and liquids to products that have been tested and found to be useful in cigarette cessation, and may also consider bans on products that are found to appeal to youth more than smokers. In sum, this study demonstrated that the electronic cigarette with and without nicotine had moderate levels of abuse liability; lower than traditional cigarettes, but higher than an FDA-approved nicotine replacement therapy (i.e., nicotine inhaler).

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APPENDIX A

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Choice assessment of nicotine-containing products in cigarette smokers

VCU IRB PROTOCOL NUMBER: HM20005746

INVESTIGATOR: Thomas Eissenberg, Ph.D.

This consent form may contain words that you do not understand. Please ask the study nurse or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE STUDY

The purpose of this study is to assess the effects of several nicotine-containing products, and the choices that participants make when asked about puffs from these products vs. money.

DESCRIPTION OF THE STUDY AND YOUR INVOLVEMENT

If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered and understand what will happen to you.

Before you join the study, we will ask you to fill out some forms about your medical history (including your use of alcohol and illicit drugs such as marijuana), and we will use breath and urine tests to make sure that you are eligible for this study. We will also ask you to practice one of the study tasks that you will be asked to complete in the study sessions. This practice task will involve choosing between a small item (such as a candy bar or pen) and varying small amounts of money. During this practice task, you may receive a small item or a small amount of money, which you will be able to keep.

If you agree to join the study, you will participate in four sessions, each taking approximately 5 hours, at the Clinical Behavioral Pharmacology Laboratory, located on VCU's medical campus. Each session will begin at approximately the same time each day, and will be separated by at least 48 hours. In addition, sessions will not occur more than twice per week. Before each session, we will ask you to abstain from all caffeine-containing beverages, and from all foods, for 1 hour. We will also ask you to abstain from all tobacco products (including e-cigarettes) and all nicotine containing products (like gum or patch) for at least 12 hours before each session. We will ask you to take a simple breath test to make sure that you have complied with these restrictions. Our tests are not perfect, but they will be the only measures that we can accept to make certain that you have complied with the no tobacco/nicotine restrictions.

At the beginning of each session, and after you provide the breath sample used to assess compliance with the no tobacco/no nicotine restrictions, a nurse will insert a thin IV catheter into your arm that will stay there until the final blood draw. This IV catheter in your arm will be used to draw blood periodically (approximately 1 tablespoon per sample, 4 samples per session). We use this method because participants tell us that it is more comfortable than repeated “sticks” with a needle. During the entire study, we will take much less blood than the amount you would give in a single donation at a blood drive. We will also ask you to participate in other procedures that include monitoring your heart rate and blood pressure and asking you to respond to several questionnaires to measure how you feel before and after each use. You will have an opportunity to review all of the questionnaires and experience all the physiological equipment before your first session.

Also, during each session, you will be asked to use a tobacco or nicotine containing product two times. This product may be an electronic cigarette, a cigarette of your own brand, or the Nicotrol inhaler. The e-cigarette may contain nicotine or no nicotine. Neither you nor the study staff will know what each e-cigarette contains. During the product use periods, you will be asked to take 10 puffs from the product, and we will instruct you when to use the product. After using the product two times, you will then be given three later opportunities to choose between puffs from the product and varying amounts of money.

After you have made your choices, one choice will be selected randomly and you will be presented with the product or money immediately. If the choice selected is product, you will be asked to use the product at that time. Thus, you will have three additional opportunities to use the product in each session. In total, you may be asked to use the product 2 – 5 times during each session. If the choice selected is money, it is yours to keep.

Lastly, any significant new findings developed during the course of the research which may relate to your willingness to continue participation will be provided to you.

RISKS AND DISCOMFORTS

You may experience some discomfort during sessions when you are not using your usual brand of cigarettes or during abstinence from cigarettes before each session. Side effects from products that contain tobacco/nicotine can include sweating, lightheadedness, dizziness, nausea, and nervousness. These effects are unlikely in individuals who use tobacco products regularly. Side effects from tobacco abstinence can include irritability, anxiety and restlessness, excessive hunger, difficulty concentrating, and sleep disturbance. Though uncomfortable, these feelings are not medically dangerous. You may also feel some discomfort when the nurse inserts or withdraws the needle, or when blood samples are taken. We try very hard to minimize your discomfort at these times, and the use of a trained nurse and sterile, disposable equipment enhances comfort while reducing the risk of bruising and infection. If you find any effects or data collection procedures unacceptable, you may stop your participation at any time. You should not donate blood 4 weeks before or 4 weeks after this study.

BENEFITS TO YOU AND OTHERS

You will receive no direct medical benefit. However, your participation will help us in the future as we try to understand the effects of different types of tobacco products.

COSTS

There is no cost to you for participation except for your time. Participating in this study will take about 20 hours in the laboratory.

PAYMENT FOR PARTICIPATION

You will be paid for the time that you are not using tobacco prior to each session and for your time in the laboratory: you will receive \$75 after completing the first session, \$125 after completing the second session, \$150 after completing the third session, and \$200 after completing the fourth session. Thus, the total amount you could earn for the entire study is \$550. In addition, during each session, you might earn additional small additional amounts of money, depending on your choices. If you choose to leave the study early, you will keep what you have earned up to that point. For example, if you complete one session, you will earn \$75.

Finally, you might earn a small amount of money (no more than \$10.24) or receive a small item (such as a candy bar or pen) during the screening visit for this study, when we ask you to practice one task that you will complete during the other sessions.

In the event a session is begun but not completed (for reasons beyond your control), you will not receive full payment for an uncompleted session. Instead, you will receive partial payment for the time spent complying with study conditions before the session began (\$15) and also for the time spent in the laboratory (\$15/hour).

Total payments within one calendar year that exceed \$600 will require the University to annually report these payments to the IRS and you. This may require you to claim the compensation you receive for participation in this study as taxable income.

You may be asked to provide your social security number in order to receive payment for your participation. Your social security number is required by federal law. It will not be included in any information collected about you for this research. Your social security number will be kept confidential and will only be used in order to process payment.

ALTERNATIVES

This is not a therapeutic study. You have the alternative not to participate.

CONFIDENTIALITY

Potentially identifiable information about you will consist of your name, birthdate, and basic demographic information. Data is being collected only for research purposes. Your data will be identified by an alphanumeric code, not names, and stored separately from research data in a

locked research area. All personal identifying information will be kept in password protected files and these files will be kept for a minimum for five years. Other records, consent forms, will be kept in a locked file cabinet for a minimum of 5 years after the study ends. All files may be kept indefinitely. Access to all data will be limited to study personnel. A data and safety monitoring plan is established.

We will not tell anyone the answers that you give us; however, information from the study and the consent form signed by you may be looked at or copied for research or legal purposes by the sponsor of the research, or by Virginia Commonwealth University. Personal information about you might be shared with or copied by authorized officials of the Department of Health and Human Services or other federal regulatory bodies.

IF AN INJURY OR ILLNESS HAPPENS

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

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

PREGNANCY

Every effort will be made to have women enter this study on an equal basis with men. Tobacco use may be harmful to a fetus, and pregnant women may not participate in this study. If you suspect that you are pregnant, or if you are currently breast-feeding a baby, please inform the investigator now and do not participate. We will conduct a urine pregnancy test during the screening evaluation to ensure that pregnant women do not participate.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

You do not have to participate in this study. If you choose to participate, you may stop at any time without any penalty. You may also choose not to answer particular questions that are asked in the study. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

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

- the study staff thinks it necessary for your health or safety;
- you have not followed study instructions;
- the sponsor has stopped the study; or
- administrative reasons require your withdrawal.

QUESTIONS

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

Principle Investigator
Thomas Eissenberg, PhD
Department of Psychology
(804)-827-3562
cstpstudies@vcu.edu

Research Nurse
Barbara Kilgalen RN
(804) 827-3562
cstpstudies@vcu.edu

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

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

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

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

CONSENT

I have been given the chance to read this consent form. I understand the information about this study. Questions that I wanted to ask about the study have been answered. My signature says that I am willing to participate in this study. I will receive a copy of the consent form once I have agreed to participate.

Participant's Printed Name

Signature of Participant

Date

Signature of Person Performing Consent

Discussion/Witness (Printed)

Signature of Person Conducting Informed Consent

Date

Discussion/ Witness's

Signature of Investigator

Date

Appendix B

Electronic Cigarette Multiple-Choice Procedure

Please Circle Your Choices:

1. 10 puffs from ECIG	\$0.01
2. 10 puffs from ECIG	\$0.02
3. 10 puffs from ECIG	\$0.04
4. 10 puffs from ECIG	\$0.08
5. 10 puffs from ECIG	\$0.16
6. 10 puffs from ECIG	\$0.32
7. 10 puffs from ECIG	\$0.64
8. 10 puffs from ECIG	\$1.28
9. 10 puffs from ECIG	\$2.56
10. 10 puffs from ECIG	\$5.12
11. 10 puffs from ECIG	\$10.24

APPENDIX C

Inhaler Multiple-Choice Procedure

Please Circle Your Choices:

1. 10 puffs from inhaler	\$0.01
2. 10 puffs from inhaler	\$0.02
3. 10 puffs from inhaler	\$0.04
4. 10 puffs from inhaler	\$0.08
5. 10 puffs from inhaler	\$0.16
6. 10 puffs from inhaler	\$0.32
7. 10 puffs from inhaler	\$0.64
8. 10 puffs from inhaler	\$1.28
9. 10 puffs from inhaler	\$2.56
10. 10 puffs from inhaler	\$5.12
11. 10 puffs from inhaler	\$10.24

APPENDIX D

Own-Brand Cigarette Multiple-Choice Procedure

Please Circle Your Choices:

1. 10 puffs from own brand	\$0.01
2. 10 puffs from own brand	\$0.02
3. 10 puffs from own brand	\$0.04
4. 10 puffs from own brand	\$0.08
5. 10 puffs from own brand	\$0.16
6. 10 puffs from own brand	\$0.32
7. 10 puffs from own brand	\$0.64
8. 10 puffs from own brand	\$1.28
9. 10 puffs from own brand	\$2.56
10. 10 puffs from own brand	\$5.12
11. 10 puffs from own brand	\$10.24

APPENDIX E

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

These phrases may or may not describe how you feel right now.
Please respond to each word of phrase with how you feel RIGHT NOW

	All	Extremely
1. Urges to use a cigarette		
2. Irritability/frustration/anger		
3. Anxious		
4. Difficulty Concentrating		
5. Restlessness		
6. Hunger		
7. Impatient		
8. CRAVING a cigarette		
9. Drowsiness		
10. Depression/ feeling blue		
11. Desire for Sweets		

APPENDIX F

Direct Effects of Product Use Scale

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

	Not at All	Extremely
1. Was the product satisfying?		
2. Was the product pleasant?		
3. Did the product taste good?		
4. Did the product make you dizzy?		
5. Did the product calm you down?		
6. Did the product help you concentrate?		
7. Did product make you feel more awake?		
8. Did the product reduce your hunger for food?		
9. Did the product make you sick?		
10. Would you like to use another product RIGHT NOW ?		

APPENDIX G

Questionnaire of Smoking Urges- Brief

For each item, please indicate how you feel RIGHT NOW

I have a desire for a cigarette right now.

Strongly disagree Strongly agree

Nothing would be better than smoking a cigarette right now.

Strongly disagree Strongly agree

If it were possible, I probably would smoke now.

Strongly disagree Strongly agree

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

Strongly disagree Strongly agree

All I want right now is a cigarette

Strongly disagree Strongly agree

I have an urge for a cigarette.

Strongly disagree Strongly agree

A cigarette would taste good now.

Strongly disagree Strongly agree

I would do almost anything for a cigarette now.

Strongly disagree Strongly agree

Smoking would make me less depressed.

Strongly disagree Strongly agree

I am going to smoke as soon as possible.

Strongly disagree Strongly agree

APPENDIX H

Direct Effects of Nicotine Scale

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

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