A BEHAVIORAL ASSESSMENT OF ELECTRONIC CIGARETTES
IN REDUCING CUE- AND WITHDRAWAL-INDUCED CRAVING
IN DAILY DEPENDENT SMOKERS

BY

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Randomized controlled trials suggest e-cigarettes may decrease cigarette craving and withdrawal symptoms, reduce cigarette smoking, and increase abstinence. However, few studies have investigated the effectiveness of non-nicotinic e-cigarettes, alone or used with nicotine replacement, in reducing craving by addressing behavioral cues.

This randomized, single-blind, within-subject study empirically assessed cigarette craving and withdrawal symptoms in 41 dependent smokers under four conditions: smoking tobacco cigarettes, non-nicotinic e-cigarettes with nicotine lozenges, non-nicotinic e-cigarettes with placebo lozenges, and using nicotine lozenges alone. While tobacco cigarettes most significantly reduced cravings one hour after smoking (-11.24±1.30, p<0.0005) as measured by the QSU-Brief, they were least effective in attenuating cue- and withdrawal-induced cravings three hours after smoking. In comparison, e-cigarettes with nicotine lozenges most effectively attenuated cue-induced (-3.24±0.84, p=0.002) and withdrawal-induced (-3.90±1.39, p=0.047) cravings while e-cigarettes with placebo lozenges and lozenges alone produced comparable craving reductions. These results suggest nicotine-free e-cigarettes decrease cigarette craving, with or without concurrent nicotine delivery.
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LIST OF ABBREVIATIONS

3HC Trans-3’-Hydroxycotinine
CO Carbon Monoxide
CYP2A6 Cytochrome P450 2A6
FTND Fagerström Test of Nicotine Dependence
IPI Interpuff Interval
nAchR Nicotinic Cholinergic Receptors
NRT Nicotine Replacement Therapy
PANAS Positive and Negative Affect Scale
QSU-Brief Brief Questionnaire of Smoking Urges
VAS Visual Analogue Scale
WHODAS World Health Organization Disability Assessment Schedule
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1. INTRODUCTION

1.1. Statement of Problem

Tobacco use is associated with a plethora of health effects and illnesses. Successful smoking cessation has been found to significantly decrease the risk of developing tobacco-related diseases. Current smoking cessation therapies focus primarily on addressing the pharmacological effects of nicotine and include nicotine replacement therapy (NRT), varenicline, and bupropion. However, rates of successful smoking cessation remain low. Electronic cigarettes (e-cigarettes) are devices initially designed to resemble tobacco cigarettes and often contain nicotine. Online surveys and recent clinical studies report that e-cigarettes may reduce tobacco craving and withdrawal symptoms and act as smoking cessation aids. However, effects are inconstant and often associated with e-cigarette user experience and highly variable nicotine delivery profiles. A better understanding of the relationship between use of e-cigarettes, cue reactivity, and craving reduction may improve our understanding of how to best use these devices for smoking cessation.

1.2. Study Purpose and Objectives

The primary objective of this study was to investigate the efficacy of e-cigarettes in alleviating craving by satiating the behavioral cues of smoking behavior, with and without concurrent nicotine administration. Within-subject differences in subjective craving and nicotine withdrawal symptoms were empirically evaluated by standardized questionnaires in e-cigarette naïve daily dependent smokers under four distinct experimental conditions: one and three hours after smoking conventional tobacco cigarettes, one and three hours after using e-cigarettes with placebo lozenges, one and three hours after using e-cigarettes with nicotine lozenges, and one and three hours after taking nicotine lozenges alone. By using a cue-reactivity procedure, changes in cue- and withdrawal-induced cravings under various conditions were subjectively assessed. Secondary objectives were to investigate differences in smoking topography between tobacco cigarettes and e-cigarettes.

1.3. Study Rationale

E-cigarettes have gained in popularity in recent years (King, Patel, Nguyen, & Dube, 2015) and users often report e-cigarettes to decrease cigarette craving and withdrawal symptoms (Etter, 2010; Etter & Bullen, 2011a). Moreover, clinical trials have reported e-cigarettes to improve rates of successful smoking cessation (Adriaens, Van Gucht, Declerck, & Baeyens, 2014; Christopher Bullen et al., 2013; Caponnetto et al., 2013). However, subjective effects of e-cigarette use have been found associated with variety of factors such as the delivery of nicotine, the primary psychoactive compound found in tobacco products associated with the behavioral and addictive properties of tobacco use (Benowitz, 2009, 2010; Guillem et al., 2005; Mansvelder & McGehee, 2002; Stoleran & Jarvis, 1995). Several variables have been also found to influence subjective measures of cigarette craving and withdrawal symptoms such as gender and user experience. Several clinical studies to date report e-cigarettes are smoked differently in
comparison to tobacco cigarettes such that, e-cigarettes require greater suction to smoke and with experience, users learn to smoke e-cigarettes more intensively to compensate (Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013b; Hua, Yip, & Talbot, 2013; Trtchounian, Williams, & Talbot, 2010). The aim of the current study was to investigate whether non-nicotinic e-cigarettes, used alone or with proven nicotine replacement therapy (NRT), can decrease cue and withdrawal-induced cigarette craving using a tobacco cue presentation procedure.

1.4. Statement and Rationale of Research Hypotheses

Since nicotine is the primary compound associated with the behavioral and addictive properties of tobacco use (Benowitz, 2009, 2010; Guillem et al., 2005; Mansvelder & McGehee, 2002; Stolerman & Jarvis, 1995), a nicotine dose-dependent reduction in cigarette craving will be observed. In other words, smoking cigarettes will produce the largest reduction in craving. Using non-nicotinic e-cigarettes with nicotine lozenges will produce the second greatest craving reduction, followed by using nicotine lozenges alone. Finally, using non-nicotinic e-cigarettes with placebo lozenges will produce the least significant reduction in cigarette craving because no nicotine will be delivered to participants. Similarly, decreases in nicotine withdrawal symptoms will be nicotine dose-dependent.

1.5. Review of Literature

1.5.1. Tobacco Use Overview

Tobacco use is the leading cause of preventable morbidity and mortality in the world (WHO, 2013). Tobacco may be consumed in a variety of forms; however, smoking tobacco cigarettes is the most common. In recent years, due to an increase in the awareness of tobacco harm, tobacco smoking has steadily decreased. In the United States, smoking in the adult population is currently 18% (Agaku, King, Dube, & (CDC), 2014; USDHHS, 2014), down by 55% since the first surgeon general’s report published 50 years ago. However, approximately 42 million adults and 3.5 million adolescents continue to smoke cigarettes in the United States alone. Similarly, between the years 1999 and 2012, the prevalence of smoking in Canadians over age 15 has decreased from 25% to 16% (HC, 2012). Unfortunately, this statistic still approximates to more than 4 million smokers. Moreover, similar decreases in the prevalence of smoking have not been observed in psychiatric populations (Cook et al., 2014). It has been estimated that 43% of individuals with unipolar depression (Pratt & Brody, 2010), 44% to 71% of individuals with bipolar disorder (Dickerson et al., 2013; Hartz et al., 2014), and 64% to 79% of individuals with schizophrenia spectrum disorders (Dickerson et al., 2013; Hartz et al., 2014) are regular smokers.

Cigarette smoke contains more than 7000 compounds, many of which are known toxins and carcinogens (ACS, 2015). Chronic exposure to tobacco smoke is associated with significantly increased risk of developing chronic obstructive pulmonary disease (COPD), coronary heart disease, stroke, cancers, and infectious diseases in comparison with non-users (Arcavi & Benowitz, 2004; Doll, Peto, Boreham, & Sutherland, 2004). More than five million deaths per year are directly related to tobacco use. Similarly,
exposure of secondhand tobacco smoke is associated with increased risks. Each year, an estimated 600,000 deaths occur as a result of secondhand smoke exposure (Oberg, Jaakkola, Woodward, Peruga, & Prüss-Ustün, 2011). Associated medical costs amount to approximately $193 billion in the United States (X. Xu, Bishop, Kennedy, Simpson, & Pechacek, 2014) and $4.4 billion in Canada each year (Rehm et al., 2006). However, the risk of developing serious diseases such as lung cancer, heart disease, and cancers have been found to decrease following cessation and sustained abstinence (Jha et al., 2013; Lightwood & Glantz, 1997; Pirie et al., 2013).

1.5.2. Pharmacology of Nicotine and Tobacco Addiction

Nicotine is the primary psychoactive compound found in tobacco products and underlies many behavioral and addictive properties of tobacco use (Benowitz, 2009, 2010; Guillem et al., 2005; Mansvelder & McGehee, 2002; Stolerman & Jarvis, 1995). Independent of tobacco, nicotine self-administration has been observed in smokers, with no intention to quit, through oral (Hughes, Rose, & Callas, 2000), nasal (Perkins, Grobe, Weiss, Fonte, & Caggiula, 1996), and intravenous (Henningfield & Goldberg, 1983) routes of administration. Moreover, greater levels of nicotine self-administration were observed in current smokers compared to non-smokers and former smokers (Hughes et al., 2000; Perkins, Gerlach, Broge, Fonte, & Wilson, 2001; Perkins, Sanders, D'Amico, & Wilson, 1997).

While nicotine may be absorbed through a variety of pathways such as transdermal or oral routes depending on the product used, nicotine inhaled from tobacco cigarette smoke is the most addictive. When cigarette smoke is inhaled, nicotine is absorbed into the pulmonary veins and quickly distributed through the arterial circulation and readily diffuses through the blood brain barrier (Benowitz, 2009).

Once in the central nervous system, nicotine stereoselectively binds to nicotinic cholinergic receptors (nAChRs) and acts as an agonist. Nicotinic cholinergic receptors are ligand-gated ion channels composed of five subunits that are found in both the peripheral and central nervous systems (Gotti, Zoli, & Clementi, 2006). While there are nine α subunits (α2 to α10) and three β subunits (β2 to β4) that may combine to form nAChRs, the most abundant receptor subtypes in humans are α4β2, α3β4, and α7. Nicotine binding results in nAChR activation, followed by a period of receptor desensitization. However, the extent to which nAChRs activate and become desensitized is dependent on receptor subunit composition (Fenster, Rains, Noerager, Quick, & Lester, 1997). Similarly, the extent and rate of recovery to a functional state is dependent on nAChR subunit composition (Alkondon & Albuquerque, 1993; Fenster et al., 1997; Ke, Eisenhour, Bencherif, & Lukas, 1998). More importantly, the α4β2 receptor subtype is most associated with the development of nicotine dependence. Animal studies have found that behavioral responses to nicotine are eliminated in β2 subunit knockout mice (Picciotto et al., 1998), while the reinsertion of subunit genes reinstates such responses (Maskos et al., 2005). Similarly, nAChRs in mice with point mutations in the α4 subunit gene are hypersensitive to nicotine (Tapper et al., 2004), suggesting the α4 subunit may influence sensitivity to nicotine, as well as the development of tolerance.
and dependence. As such, current pharmacotherapies for smoking cessation focus on modulating the mechanism of action of nicotine.

However, nicotine is a lipid-soluble tertiary amine alkaloid that is extensively metabolized in the liver and lungs by cytochrome P450 2A6 (CYP2A6) enzymes into cotinine (Benowitz, Hukkanen, & Jacob, 2009; Hukkanen, Jacob, & Benowitz, 2005). While the half-life of nicotine is approximately 2 hours, that of cotinine is 16 hours and levels are often stable throughout the day. As a result, cotinine is often used as a biomarker for tobacco use. Cotinine may then be metabolized by CYP2A6 into trans-3'-hydroxycotinine (3HC). Nicotine and cotinine may also undergo glucuronidation by enzymes UGT 1A4, 1A9, and 2B10. Moreover, nicotine metabolism is influenced by a variety of factors such as genetics and environment (Benowitz, Swan, Jacob, Lessov-Schlaggar, & Tyndale, 2006; Ray, Tyndale, & Lerman, 2009; Swan et al., 2004).

The metabolism and elimination of nicotine is of concern as drug abuse liability is associated with the rate of distribution, absorption, and elimination (Henningfield & Keenan, 1993) such that faster rates of delivery and higher peak plasma concentrations have been associated with greater abuse liability. Nicotine delivery from cigarette smoke to the brain occurs within approximately 10 to 15 seconds and a half-life of 2 hours (Benowitz, 1988) while nicotine delivered from transdermal patches has a half-life of 4 hours (Palmer, Buckley, & Faulds, 1992). Moreover, cigarette smoke delivers a higher dose of nicotine than other tobacco products such as oral snuff, chewing tobacco, nicotine gum, and nicotine patch (Benowitz, 1988; Benowitz, Chan, Denaro, & Jacob, 1991). As a result, due to the faster rates of absorption and distribution as well as higher plasma nicotine concentrations achieved, nicotine inhaled from cigarette smoke is more addictive than that derived from other tobacco products. However, in addition to the pharmacokinetics of nicotine, the pharmacodynamics, reinforcing effects, and adverse effects all contribute to the abuse liability of tobacco products (L. P. Carter et al., 2009).

1.5.3. Psychoactive Effects of Nicotine

When bound to nAchR, brain imaging studies have found nicotine to increase activity in the prefrontal cortex, thalamus, and visual system through the release of various neurotransmitters including dopamine, norepinephrine, and serotonin (Brody, 2006). More importantly, nicotine binding to nAchRs in the central nervous system results in dopamine release in the ventral tegmental area of the midbrain and the nucleus accumbens (Dani & De Biasi, 2001). Moreover, administration of central nicotine antagonist mecamylamine increases smoking behavior while treatment with peripheral antagonist pentolinium produces no significant differences (Stolerman, Goldfarb, Fink, & Jarvik, 1973).

Various mechanisms contribute to nicotine-mediated activation of the dopamine system. Nicotine mediates glutamatergic projections to enhance activation of dopaminergic neurons in the ventral tegmental area (Mansvelder & McGehee, 2002). Conversely, nicotine stimulates GABAergic projections to inhibit dopaminergic neuron activation. It is through the interplay between various pathways that
nicotine mediates the activity of the mesolimbic dopamine system, a critical component of the rewarding, reinforcing, and addictive properties of nicotine (Balfour & Fagerström, 1996).

1.5.3.1. **Acute Nicotine Exposure**

Acute nicotine exposure results in rapid nAChRs activation and subsequent receptor desensitization (Dani & Heinemann, 1996).

Increased heart rate, blood pressure, and improved psychomotor activity and cognition are among some effects of nicotine. Additionally, nicotine stimulates rewarding effects such as pleasure and reduces stress and anxiety. As a result, smokers are able to modulate their mood and performance by titrating their plasma nicotine concentration from cigarette smoking.

1.5.3.2. **Chronic Nicotine Exposure**

With prolonged and repeated nicotine exposure, neuroadaptations develop and contribute to the development of tolerance and dependence (Wang & Sun, 2005). Regular daily smokers often maintain complete $\alpha_4\beta_2$ nAchR saturation, causing receptors to become desensitized following prolonged activation (Brody et al., 2006). In order to compensate for attenuated receptor desensitization as a result of prolonged nicotine exposure, an increase in the number of nAchR is often observed (Dani & Heinemann, 1996; Marks, Burch, & Collins, 1983). Craving and withdrawal symptoms arise when previously desensitized nAchRs become unoccupied during periods of smoking abstinence and recover to a responsive state (Dani & Heinemann, 1996).

1.5.4. **Withdrawal Symptoms**

Contrary to the stimulant effects of nicotine, withdrawal symptoms often include negative emotional states such as anxiety and increased stress. During periods of smoking abstinence, withdrawal symptoms emerge including mood disturbances, irritability, anxiety, difficulty concentrating, anhedonia, and craving (Hughes & Hatsukami, 1986; Koob & Le Moal, 1997).

As with all substances of abuse, the basis of tobacco addiction may be resultant from both positive reinforcements, such as enhanced mood and cognition, and negative reinforcements in the form of withdrawal symptoms.

While nicotine is the primary addictive component of tobacco cigarettes, it has minimal effects in increasing the risks of developing smoking-related diseases (Ambrose & Barua, 2004; Lúdvíksdóttir, Blöndal, Franzon, Gudmundsson, & Säwe, 1999; Nitenberg & Antony, 1999; Zevin, Jacob, & Benowitz, 1998). For example, a study in smokers with established cardiovascular diseases found that nicotine exposure through nicotine replacement therapy (NRT) did not increase cardiovascular risk (Woolf et al., 2012). As a result, products either delivering nicotine through non-combustion pathways or modulating
nicotine binding are expected to have significantly lower health risks in comparison to smoking tobacco products and have been the focus of developing smoking cessation treatments.

1.5.5. **Current Treatments of Tobacco Addiction**

Current pharmacotherapy for tobacco dependence may be categorized as first-line or second-line treatments. First-line treatments include nicotine replacement therapy (NRT), varenicline, and bupropion while second-line pharmacotherapies include clonidine and nortriptyline.

1.5.5.1. **Nicotine Replacement Therapy (NRT)**

As previously mentioned, nicotine is the primary addictive component of tobacco products; however, nicotine alone is not known to cause adverse health effects. While observational studies have suggested nicotine during pregnancy may be associated with increased risk of low birth weight and preterm births, findings are severely limited due to a plethora of confounding factors not taken into consideration (Inamdar, Croucher, Chokhandre, Mashyakhy, & Marinho, 2014).

Nicotine replacement therapy (NRT) was the first effective pharmacological treatment for tobacco dependence and remains the most common first-line medication used for smoking cessation and management of withdrawal symptoms (Hughes, 2013). The primary mechanism of action of NRT is to provide partial amounts of nicotine, compared to that from cigarette smoking, to reduce the severity of craving and withdrawal symptoms during periods of smoking abstinence (R. J. West, Jarvis, Russell, Carruthers, & Feyerabend, 1984). NRT is available in a variety of formulations such as gums, transdermal patches, lozenges, and inhalers. While differences in formulations are associated with varying efficacies, all approved NRT are found to significantly increase the probability of successful quit attempts and maintaining long-term smoking abstinence in comparison to placebo (Stead, Perera, Bullen, Mant, & Lancaster, 2008). Moreover, since absorption of nicotine from NRT is slower than that from tobacco cigarettes, NRT does not produce much of the positive reinforcing effects associated with cigarette smoking and is found to have lower potential of dependence and abuse liability (Le Houezec, 2003; R. West et al., 2000). NRT is also generally associated with low rates of adverse events (Hajek et al., 1999).

While nicotine pretreatment using nasal sprays attenuates smoking behavior, the decreased magnitude of smoking suppression in comparison to cigarette smoking suggests factors other than nicotine may contribute to smoking behavior (Perkins, Grobe, Stiller, Fonte, & Goettler, 1992).

1.5.5.2. **Varenicline**

Varenicline (Chantix, Champix®) is a selective partial agonist for α4β2 nicotinic acetylcholine receptors (nAchRs). The efficacy of varenicline as a smoking cessation aid can be attributed to its ability to both partially stimulate nAchRs (agonist) and competitively block nicotine from tobacco products from binding.
to nAchRs (antagonist) (Coe et al., 2005; Rollema et al., 2007). Through partial activation of α₄β₂ nAchRs, varenicline produces moderate elevation in dopamine levels in reward pathways while preventing nicotine-induced dopaminergic activation. Moreover, varenicline is a full and potent agonist of homomeric α₇ nAchRs (Mihalak, Carroll, & Luetje, 2006) that have been associated with decreasing motivation to self-administer nicotine (Brunzell & McIntosh, 2012). Treatment has generally been well tolerated, with minimal adverse events, and no known contraindications (Potts & Garwood, 2007). Moreover, with the exception of alcohol, no clinically significant drug interactions have been observed to date (FDA, 2015). However, varenicline has been associated with increased risk of depressed mood and suicidal ideation and behavior (Cahill, Stead, & Lancaster, 2009); therefore medication labels include a boxed warning.

1.5.5.3. **Bupropion**

Bupropion hydrochloride was initially developed and marketed as an antidepressant, but later found to be an effective smoking cessation aid by blocking the reuptake of dopamine and norephinephrine in reward systems (Wilkes, 2008) and acting as an antagonist at nAchR to block some reinforcing effects of nicotine (Crooks, Bardo, & Dwoskin, 2014). Moreover, bupropion has also been found to reduce smoking craving and withdrawal symptoms (Mooney & Sofuoglu, 2006). The efficacy of bupropion has been found to be equal to that of NRT but lower than that of varenicline (Gonzales et al., 2006; Jorenby et al., 2006). However, seizures and hypersensitivity reactions have been reported as infrequent adverse reactions to bupropion. As a result, the treatment is contraindicated for many individuals including those who have a history of seizure disorders, cardiovascular conditions, and hypersensitivity to the medication. Moreover, similar to varenicline, equivocal findings have suggested an association between bupropion and increased risk of depression and suicidal behavior (Moore, Furberg, Glenmullen, Maltsberger, & Singh, 2011; Wightman, Foster, Krishen, Richard, & Modell, 2010); therefore the medication includes a black label warning in that regard.

Despite having a multitude of treatment options, tobacco remains the leading preventable cause of morbidity and mortality. 80% of smokers who attempt to quit smoking themselves relapse to smoking within one month and only 3% successfully quit each year (Benowitz, 2010). With the aid of smoking interventions, individuals are more likely to achieve smoking abstinence; however, rates of successful quit attempts remain low (Johnson, 2010). As such, future research should focus on personalizing current treatment options to enhance efficacy as well as exploring new treatment options by addressing other factors contributing to the development of drug addiction. Theories of drug dependence speculate that cravings are associated with dependence and contribute to motivating drug use (Drummond, 2001). As such, drug cravings may be obstacles of successful quit attempts. However, the precise role of drug craving in addiction remains poorly understood.
1.5.6. **Conditioned Cues**

In addition to the psychoactive effects of nicotine, conditioned cues are thought to contribute to cigarette smoking even during periods of nAChR saturation and desensitization (Balfour, 2004; Donny et al., 2003). Conditioning develops when the pharmacological effects of the drug become coupled with stimuli and cues. In other words, with repeated exposure, substance users learn to associate the rewarding effects of drugs with internal cues such as mood states, as well as external cues such as environments and social situations. For example, for an individual who smokes after meals or whilst drinking with friends, such environmental situations may become powerful cues to smoke. Similarly, handling of cigarettes and smoking paraphernalia become associated with the rewarding effects of smoking.

As previously mentioned, nicotine is the primary component of tobacco reinforcing smoking behaviors (Stolerman & Jarvis, 1995) and has been found to be particularly salient at associating incentive properties and reinforcing effects to non-pharmacological neutral stimuli (Goldberg, Spealman, & Goldberg, 1981; Rose & Levin, 1991).

Once established, conditioned smoking cues may contribute to smoking by continuing to produce rewarding effects from conditioned reinforcers associated with smoking (Balfour, 2004). For example, studies have found subjective craving and withdrawal after smoking denicotinized cigarettes to be comparable to that of smoking regular nicotine cigarettes (Butschky, Bailey, Henningfield, & Pickworth, 1995; Gross, Lee, & Stitzer, 1997). In addition to rewarding effects, conditioned cues have also been associated with stimulating cigarette craving and relapse during periods of smoking abstinence, even after initial withdrawal symptoms subside during a quit attempt (B. L. Carter & Tiffany, 1999; Ferguson & Shiffman, 2009). Cigarette cravings are often associated with a higher likelihood of smoking behavior (Bagot, Heishman, & Moolchan, 2007; Tiffany, Warthen, & Goedeker, 2009; Tiffany & Wray, 2009) and craving intensity during the first days of smoking abstinence is predictive of quit attempt success (Ferguson, Shiffman, & Gwaltney, 2006). As a result, it has been suggested that addressing the sensory, behavioral, and environmental cues related to smoking may reduce tobacco craving and withdrawal symptoms (Hajek, Jarvis, Belcher, Sutherland, & Feyerabend, 1989; Rose & Levin, 1991).

1.5.7. **Cigarette Craving**

Many theories of drug dependence speculate that cravings are associated with dependence and contribute to motivating drug use (Drummond, 2001). Since drug craving is often associated with a higher likelihood to smoke, it is considered an obstacle of successful quit attempts (Bagot et al., 2007; Tiffany et al., 2009; Tiffany & Wray, 2009). Moreover, cravings may occur even after long periods of abstinence (Hughes, 2010). However, the precise role of drug craving in addiction remains unclear.

Cravings may be categorized into two varieties. Gradual fluctuations over the course of a day are commonly referred to as general levels of craving and are likely a result of prolonged periods of
abstinence between cigarettes (Schuh & Stitzer, 1995). Studies have detected increases in craving one hour after smoking abstinence (Tiffany & Drobes, 1991) and cravings continue to rise to relatively elevated levels within three to six hours following the beginning of abstinence (Drobes & Tiffany, 1997; Maude-Griffin & Tiffany, 1996; Schuh & Stitzer, 1995; Tiffany & Drobes, 1991). Cue-specific cravings refer to responses to smoking-related cues that have been paired the rewarding effects of nicotine (B. L. Carter & Tiffany, 1999; Tiffany & Wray, 2009). Cue-induced cravings have a fast onset and are often transient. Similarly, general cravings are usually transient and do not reach peak intensity during regular smoking days since cravings are alleviated by periodic nicotine administration from smoking. However, the intensity and duration of general cravings increases during quit attempts. The cumulative effect of both general and cue-induced cravings, particularly during quit attempts and periods of smoking abstinence, have been associated with the risk of relapse (Drummond, Litten, Lowman, & Hunt, 2000). Prospective studies have found smokers with high levels of cigarette craving during smoking abstinence are more than twice as likely to relapse as smokers with low levels of cigarette craving (Killen & Fortmann, 1997). Moreover, craving intensity during the first days of smoking abstinence is suggested to be predictive of quit attempt success (Ferguson et al., 2006).

1.5.8. **Cue-Reactivity and Cue-Induced Cravings**

The positive-incentive model postulates that the incentive value of paired cues will increase during periods of smoking abstinence such that abstinent smokers will be more sensitive to smoking cues (Baker, Morse, & Sherman, 1986; Stewart, de Wit, & Eikelboom, 1984). However, several studies have found that despite smoking abstinence-induced elevation in cravings, abstinent smokers are not more sensitive to cues (Drobes & Tiffany, 1997; Maude-Griffin & Tiffany, 1996). Nonetheless, once coupled with drug use, cues may then stimulate drug craving (B. L. Carter & Tiffany, 1999; Ferguson & Shiffman, 2009) and increase the intensity of urges to smoke (Lazev, Herzog, & Brandon, 1999) as well as time spent puffing on cigarettes (Mucha, Pauli, & Angrilli, 1998).

Cue-reactivity paradigms involve presenting drug-related stimuli to individuals with a history of drug use to monitor responses including the activation of motivational processes that contribute to maintaining drug use (Tiffany et al., 2009). Paradigms evaluate physiological, behavioral, and subjective responses, such as heart rate and drug craving, to conditioned drug-related stimuli in laboratory environments (B. L. Carter & Tiffany, 1999).

Studies have reported visual smoking-related cues to produce robust increases in craving and changes in mood and autonomic responses in comparison to neutral cues (B. L. Carter & Tiffany, 1999; Maude-Griffin & Tiffany, 1996; Tiffany & Drobes, 1990; Tiffany & Hakenewerth, 1991). Moreover, subjective craving has been found to reach similar levels following presentation of *in vivo* cues, such as watching someone light and smoke a cigarette (Drobes & Tiffany, 1997). As a result, both images and tactile stimuli are often used concurrently to evaluate cue reactivity.
Most studies utilizing the cue-reactivity paradigm have been conducted in laboratory settings. *Warthen et al* conducted a study to investigate the use of the cue reactivity paradigm in the natural environment using the cue-reactivity ecological momentary assessment (CREMA) (Warthen & Tiffany, 2009). In addition to laboratory visits, participants were given personal digital assistant computers to complete real-time assessments in the event of a cue in their real-world settings. Investigators reported the CREMA procedure to be effective at monitoring craving in real-world environments such that cravings were significantly higher following smoking-related cues in comparison to neutral cues. Moreover, cue-induced cravings were found to have similar effect sizes in the laboratory and natural environments. As such, CREMA may be used to investigate changes in cue-induced cravings in real-world settings.

1.5.8.1. **Animal Studies**

Animal studies often implement a conditioned reinforcement paradigm to investigate cue-induced drug seeking behavior during which nicotine administration is first paired with one or more neutral stimuli such as light or sound cues (Donny et al., 2000).

Studies have found nicotine-paired cues to sustain self-administration behavior at levels similar to nicotine administration itself (Caggiula et al., 2001). However, the level of self-administration behavior was lower than when cues and nicotine are combined. Moreover, in addition to maintaining self-administration behaviors, nicotine-paired cues may promote the reacquisition of behaviors after extinction. In a subsequent study, rats receiving conditioned cues and nicotine acquired self-administration behavior more rapidly than animals receiving only nicotine (Caggiula et al., 2002). The reinforcing effects of 0.03mg/kg nicotine were weak in the absence of paired cues. However, when light cues and the same nicotine dose were presented, animal self-administration was significantly higher. As a result, investigators concluded that while nicotine itself has reinforcing effects, paired cues may also be necessary in the acquisition and maintenance of drug use. Similarly, another study investigated the effects of environmental and conditioned cues on nicotine relapse in rats and reported cues may modulate the extinction and reacquisition of nicotine-seeking behavior (Wing & Shoaib, 2008). Extinction was quicker when animals were placed in a novel environment in comparison to the environment in which the animals underwent self-administration training. Moreover, a significant reinstatement effect was observed following the reintroduction of drug cues. Findings from these studies suggest nicotine-paired cues contribute to maintaining and reinstating drug-seeking and self-administration behaviors.

Conversely, another study investigated the effects of stimuli associated with withdrawal (Kenny & Markou, 2005). Investigators paired light and tone stimuli with nicotine withdrawal in rats and measured intracranial self-stimulation thresholds in the brain. Withdrawal-paired stimuli significantly decreased activity in the brain reward systems to levels found during unconditioned nicotine withdrawal. Moreover, conditioned cues elevated reward thresholds. Therefore stimuli associated with withdrawal may potentiate the magnitude of nicotine withdrawal and decrease rewarding effects in nicotine-dependent
ruths. In other words, conditioned stimuli in animals may potentiate drug-seeking and drug-taking behavior by promoting self-administration and reinforcing effects as well as precipitating the negative affect of withdrawal.

1.5.8.2. Human Studies

In addition to animal studies, many human studies have investigated the importance of conditioned cues in perpetuating smoking behavior. Interestingly, due to its distinctive taste and irritant properties, nicotine itself has been found to act as a sensory cue for the subsequent pharmacological effects (Herskovic, Rose, & Jarvik, 1986; Rosecrans, 1979). As a result, it is a challenge for many studies to dissociate the effects of nicotine as a sensory cue and the pharmacological effects of nicotine.

While nicotine gum and transdermal nicotine patches improve the rates of successful smoking cessation, use has not been found to significantly reduce cigarette craving (Hughes et al., 1984). One study compared transdermal nicotine and placebo patches and reported no significant differences in cigarette craving reductions (Rose, Levin, Behm, Adivi, & Schur, 1990). In comparison to smoking tobacco cigarettes, intravenous injections of 0.75 mg nicotine produced no significant effects on the desire to smoke (Henningfield, Miyasato, & Jasinski, 1985).

Tiffany et al. investigated changes in cue-induced craving in abstinent smokers after using transdermal nicotine patches (Tiffany, Cox, & Elash, 2000). Sets of neutral and smoking-related images and in vivo cues were presented to 61 smokers during two study sessions. The sessions were spaced six hours apart during which participants used placebo or nicotine transdermal patches. Investigators found nicotine patches to reduce smoking abstinence-induced craving. These findings are congruent to previous studies reporting transdermal nicotine patches to decrease general craving following 90 minutes (Rose, Herskovic, Trilling, & Jarvik, 1985) and 24 hours (Leischow et al., 1997) of smoking abstinence. However, nicotine transdermal patches produced no significant effect on cue-induced cravings. Since cue-induced cravings contribute significantly to overall craving experienced by smokers during cessation attempts, these finding suggest levels of craving remain elevated despite nicotine replacement therapy.

In addition to visual cues, smokers have been found to respond to tactile cues. A study found subjective craving and withdrawal after smoking denicotinized cigarettes to be comparable to that of smoking regular nicotine cigarettes (Butschky et al., 1995; Gross et al., 1997). Moreover, smoking satisfaction of denicotinized cigarettes has been associated with levels of dependence, wherein more tobacco dependent smokers derived greater satisfaction (Brauer et al., 2001).

Reductions in subjective craving and withdrawal reported by smokers following administration of irritants that provide throat sensations such as citric acid aerosol (Rose & Hickman, 1987) and black pepper extract (Rose & Behm, 1994) were similar to those of tobacco cigarette smoking. Similarly, satisfaction
from using an inhaler delivering a citric acid aerosol has been correlated with the intensity of throat sensations (Levin, Rose, & Behm, 1990). A randomized, placebo-controlled trial was conducted comparing the rates of smoking abstinence after using citric acid inhalers with nicotine patches and placebo inhalers with nicotine patches for 10 weeks and found continuous smoking abstinence was found to be higher in the citric acid inhaler group (Westman, Behm, & Rose, 1995).

Similarly, various studies have manipulated the nicotine-to-tar ratio to investigate the influence of sensory cues on satisfaction and craving. Since tar reduces the irritant properties of nicotine, increasing the nicotine-to-tar ratio has been found to increase puff satisfaction and perceived strength (Herskovic et al., 1986; Hughes et al., 1984).

Conversely, studies have been conducted to investigate the effects of blocking cues. An early study removed sensory cues by applying local anesthetics to the respiratory airway (Rose, Tashkin, Ertle, Zinser, & Lafer, 1985). Even while using tobacco cigarettes, smokers reported lower levels of smoking satisfaction. When olfactory cues were blocked with nose clips, participants reported reduced taste and enjoyment (Baldinger, Hasenfratz, & Bättig, 1995). Another study reported significantly reduced satisfaction and attenuated smoking behavior when visual and olfactory cues were blocked using goggles and nose clips (Perkins, Gerlach, Vender, et al., 2001).

To dissociate the relative importance of cues and nicotine doses in smoking reward, a study measured the immediate subjective responses to cues and nicotine administration separately and in combination (Rose, Behm, Westman, & Johnson, 2000). Participants were randomized into three groups to receive continuous intravenous nicotine, pulsating intravenous nicotine, or saline. Responses were measured after smoking a denicotinized cigarette and again while not smoking. A fourth group receiving saline infusions and smoking their normal cigarettes was included as control. Denicotinized cigarettes significantly reduced craving and was rated significantly more rewarding than not smoking. Moreover, while nicotine intravenous infusions reduced craving, no significant differences were observed in ratings of satisfaction and reward in comparison to saline infusions, suggesting smokers require both sensory cues and nicotine to experience smoking rewards and reduce craving. Similar to the findings in animal studies, results of human trials suggest nicotine-paired stimuli contribute to cigarette craving and subsequently, smoking behaviors.

Cue-induced cravings reflect an individual’s responsiveness to behavioral and environmental cues. It has been suggested that smokers with more intense cue-induced cravings have greater difficulty quitting smoking and a higher likelihood of relapse (Drummond et al., 2000). As such, cue-induced cravings may predict successful smoking cessation (Ferguson & Shiffman, 2009). However, due to inconsistent study designs and limitations, the degree to which cue-induced cravings influence the rate of successful quit attempts and the risk of relapse remains highly controversial (Perkins, 2009, 2012; Wray, Gass, & Tiffany, 2013).
1.5.9. **Gender Differences**

As previously mentioned, nicotine is primarily metabolized by cytochrome P450 2A6 (CYP2A6) enzymes into cotinine (Benowitz & Jacob, 1994; Messina, Tyndale, & Sellers, 1997). CYP2A6 is also responsible for the metabolism of cotinine to 3'-trans-hydroxycotinine (Nakajima et al., 1996). Nicotine and cotinine may also undergo N-glucuronidation while 3'-trans-hydroxycotinine undergoes O-glucuronidation for elimination (Benowitz & Jacob, 1994).

Past studies have found that women metabolize nicotine more quickly than men. When compared to men with similar levels of cigarette consumption, the plasma nicotine concentrations in women have been found to be significantly lower (Zeman, Hiraki, & Sellers, 2002).

Several studies have suggested the more rapid rate of metabolism may be a result of increased CYP2A6 activity and increased N-glucuronidation. One study reported rates of nicotine metabolism to significantly increase during pregnancy (Dempsey, Jacob, & Benowitz, 2002). Similarly, the rate of cotinine clearance was also substantially increased during pregnancy, decreasing the half-life of cotinine from 17 hours in non-pregnant adults to less than 9 hours in pregnant smokers. In a subsequent study, investigators found female sex hormones, namely estrogen, to induce faster nicotine metabolism (Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006). Women were observed to metabolize nicotine faster than males, and women taking oral contraceptives metabolized nicotine more readily than those who did not. Moreover, in comparison to participants who did not use oral contraceptives or used hormone replacement therapy, individuals using combined and estrogen-only contraceptives were found to metabolize nicotine more rapidly while those using progesterone-only contraceptives metabolized nicotine more slowly. Post-menopausal women were found to metabolize nicotine similarly to men. And another study reported the phase of menstrual cycle to not significantly affect nicotine or cotinine clearance (Hukkanen, Gourlay, Kenkare, & Benowitz, 2005).

Since tobacco cigarette smokers have been shown to titrate use and maintain desired levels of nicotine, faster nicotine metabolism in female smokers has been associated with greater cigarette consumption or smoking cigarettes more intensively (Tyndale & Sellers, 2002). Moreover, faster metabolism has been linked with lower rates of successful cessation. Several smoking cessation trials have reported women to have lower rates of successful smoking cessation with nicotine replacement therapy (NRT) in comparison to men (Bjornson et al., 1995; Gourlay, Forbes, Marriner, Pethica, & McNeil, 1994; Swan, Jack, & Ward, 1997). Despite NRT being shown effective as smoking cessation aids in males and females, several studies have reported NRT to more greatly suppress withdrawal symptoms and reduce craving in males (Killen, Fortmann, Newman, & Varady, 1990; Wetter et al., 1999).

Moreover, studies have reported women to be more sensitive to the non-nicotinic effects and stimuli of smoking (Perkins, Donny, & Caggiula, 1999; Perkins et al., 1994). One study investigated the effects of visual and olfactory stimuli on acute subjective and reinforcing effects of smoking in men and women.
(Perkins, Gerlach, Vender, et al., 2001). Participants attended two visits during which they smoked cigarettes from their preferred brand. During one of the two sessions, participants wore opaque goggles and nose clips to block smoking stimuli. Subjective ratings of reinforcing effects were significantly reduced during blockage of cigarette smoking stimuli. However, perceptual ratings of cigarettes such as nicotine strength were unaffected by blocking stimuli. Findings indicated that visual and olfactory stimuli significantly affected puff self-administration and subjective ratings in women only. Similarly, a study of denicotinized cigarettes observed women to report greater reductions in craving (Barrett, 2010).

In comparison to men, women have also been found to be more sensitive to the negative subjective effects of nicotine when nicotine administered intravenously (Sofuoglu & Mooney, 2009), through nasal sprays (Myers, Taylor, Moolchan, & Heishman, 2008), or while using various doses of transdermal nicotine patches (Evans, Blank, Sams, Weaver, & Eissenberg, 2006; Kleykamp, Jennings, Sams, Weaver, & Eissenberg, 2008). Conversely, women are less sensitive to the reinforcing effects of nicotine in comparison to men (Perkins et al., 2009) while men are more discerning of nicotine doses (Perkins, Jacobs, Sanders, & Caggiula, 2002) such that nicotine derived from cigarettes influenced subjective and reinforcing effects to a lower extent in women than in men.

Investigations of gender differences on withdrawal effects have reported equivocal findings. Two laboratory studies mentioned earlier reported no significant interactions between gender and withdrawal symptoms (Evans et al., 2006; Kleykamp et al., 2008). More recently, a study aimed to investigate gender differences in response to low nicotine cigarette and NRT (Vogel et al., 2014). Participants were randomized to use low nicotine yield cigarettes, nicotine patch, or both products for 6 weeks. Investigators found gender differences in responses of satisfaction, craving, cigarettes smoked, and withdrawal. Males using both nicotine patches and low nicotine yield cigarettes reported greater satisfaction than those using only cigarettes. However, in females, concurrent product use was associated with reduced satisfaction in comparison to using only low nicotine yield cigarettes. Similarly, males experienced greater suppression of withdrawal when using both nicotine patches and low nicotine yield cigarettes while females using both products reported no greater withdrawal symptom reduction than those using only cigarettes. Males using the nicotine patch were found to have higher abstinence rates than females assigned to the same conditions.

Another study evaluated differences in mood, cigarette craving, and withdrawal symptoms following periods of smoking abstinence (J. Xu et al., 2008). Participants attended two study visits and were instructed to arrive to one visit overnight smoking abstinent and arrive to the other having smoked ad libitum until 15 to 60 minutes prior to the study. After completing baseline questionnaires, participants smoked one cigarette and completed a second set of questionnaires. Investigators found women reported higher greater negative affect scores following overnight smoking abstinence. Moreover, in comparison to men, women reported greater levels of relief from withdrawal symptoms after smoking one cigarette.
Moreover, during smoking abstinence, men have significantly higher availability of $\beta_2$ subunit nicotine acetylcholine receptors in comparison to women, suggesting nicotine may affect the receptors differently between genders (Cosgrove et al., 2012).

Despite all of the research documenting gender differences in reactivity to nicotine, many report mixed findings regarding gender differences in withdrawal relief. Since the studies investigated withdrawal relief from different routes of nicotine administration, the equivocal findings may be a result of varying nicotine delivery profiles.

In summary, despite the availability of various treatment options, rates of successful quit attempts are low. Findings to date suggest tobacco craving and withdrawal symptoms may be reduced by addressing sensory, behavioral, and environmental cues related to cigarette smoking (Hajek et al., 1989; Rose & Levin, 1991). However, current smoking cessation treatment options do not address sensorimotor behavioral cues associated smoking.

1.5.10. **Electronic Cigarettes (E-Cigarettes)**

1.5.10.1. **Background, Awareness, and Use**

Electronic cigarettes (e-cigarettes) or electronic nicotine delivery devices (ENDS) often consist of a cartridge, liquid, an atomizer or cartomizer, a lithium ion battery, and a microchip. When users inhale on the mouthpiece, the microchip and atomizer are activated to vaporize the cartridge liquid. Cartridge liquids (e-liquids) commonly contain humectants such as propylene glycol and glycerol, flavoring, and nicotine. The amount of nicotine in e-liquids depends on the e-cigarette brand and type; however, liquids not containing nicotine are also widely available.

Since their invention and development in 2004 by the Chinese group Ryugan (Yamin, Bitton, & Bates, 2010), e-cigarettes have increasingly gained in popularity worldwide (Etter & Bullen, 2011a; Hajek, Etter, Benowitz, Eisenberg, & McRobbie, 2014; King et al., 2015; Palipudi et al., 2015). From 2009 to 2013, ever-use of e-cigarettes by the U.S. adult population increased from 1% to 8.5% (King et al., 2015; Regan, Promoff, Dube, & Arrazola, 2013). From 2009 to 2013, ever-use of e-cigarettes by the U.S. adult population increased from 1% to 8.5% (King et al., 2015; Regan, Promoff, Dube, & Arrazola, 2013). Similarly, the use of e-cigarettes has escalated at an alarming rate in youth. A nationwide survey in the U.S. reported 13.4% of high school students (approximately 2 million youth) have used an e-cigarette within the past 30 days (Arrazola et al., 2015). More alarmingly, a non-linear increase in e-cigarette use was observed between 2011 and 2014, during which use increased from 1.5% to 13.4% in the youth population, overtaking tobacco cigarettes as the most common nicotine product used. Similarly, a study in 2892 Ontario high school students revealed 15% of students have used e-cigarettes in their lifetime (Hamilton et al., 2014). Despite regulations preventing the sale of e-cigarettes containing nicotine in Canada, 28% of students reported having used nicotinic e-cigarettes. Moreover, 7% of students reporting never having smoked tobacco cigarettes have used e-cigarette. More recently, a survey of 44,163 high school students enrolled in COMPASS, a cohort study
of 89 sampled secondary schools in Ontario and Alberta, reported 7.2% of the sample had used an e-cigarette in the past month (Czoli, Hammond, Reid, Cole, & Leatherdale, 2015).

As mentioned, all e-cigarettes comprise of similar components such as a cartridge, e-liquid, an atomizer, and a lithium battery; however, individual devices are highly variable and are often categorized into three types. Initial e-cigarette designs often resemble tobacco cigarettes. Known as “first-generation” devices, these e-cigarettes contain disposable or rechargeable batteries and a combined cartridge and atomizer unit, a cartomizer. “Second-generation” e-cigarettes offer users opportunities to customize their devices and rarely resemble tobacco cigarettes in appearance. These newer devices often comprise of larger batteries, offering higher voltage options, and refillable cartridges. The newest in e-cigarette offerings are often referred to as “third generation” devices and offer users the greatest amount of personalization. Users are able to customize power-adjustable and programmable batteries and the atomizer heating coils and wicks to adjust output voltages and liquid vaporization temperatures to their liking.

As previously discussed, studies have found sensory stimulation and simulation of smoking behavior to be important factors contributing to a product’s effectiveness as a smoking reduction or cessation aid (Hajek et al., 1989; Rose & Levin, 1991). However, current NRT and medications for smoking cessation lack such features. E-cigarettes are unique in that, in addition to potentially delivering nicotine, they allow users to simulate smoking behaviors such as exhaling smoke and the hand-to-mouth motion (Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013a). For this reason, e-cigarettes may be potential smoking cessation aids. However, research to date has reported equivocal findings and further investigation is required.

1.5.10.2. Retrospective Surveys

Many retrospective studies have reported use of e-cigarettes effective in decreasing tobacco craving and withdrawal symptoms (C. Bullen et al., 2010; Dawkins, Turner, Roberts, & Soar, 2013; Etter, 2010; Etter & Bullen, 2011a; Vansickel, Cobb, Weaver, & Eissenberg, 2010). Moreover, users often report e-cigarettes to be effective smoking cessation aids or substitutes for tobacco cigarettes. An online survey characterized the subjective effects of e-cigarette use on 1347 e-cigarette users around the world (Dawkins et al., 2013). While 14% of participants reported their cigarette consumption decreased since use, 74% of participants reported not smoking for several weeks to months since using e-cigarettes. Furthermore, 91% of participants associated e-cigarette use with cigarette craving reduction.

1.5.10.3. Nicotine Yield and Delivery

The effectiveness of e-cigarettes as smoking cessation aids may partially depend on their ability to deliver nicotine to the brain. Moreover, the abuse liability of e-cigarettes is a topic of concern and factors contributing to a product’s abuse potential include pharmacokinetics, pharmacodynamics, reinforcing
effects, and adverse effects (L. P. Carter et al., 2009). As a result, the pharmacokinetics of nicotine from e-cigarettes remains a focus of investigation.

Early studies have observed highly variable nicotine yields. In 2009, the FDA investigated nicotine yields in 100ml puffs from 18 brands and models of e-cigarettes and found actual nicotine levels were inconsistent with labeled quantities (Westenberger, 2009). For example, a nicotine yield of 0.35μg/100ml puff was identified in e-cigarettes listed as containing no nicotine. Similarly, a study of 8 e-cigarettes with nicotine labels ranging from 11 to 24mg/cartridge found cartridge nicotine levels ranging from 0mg/cartridge to 21.0mg/cartridge and nicotine yields ranging from 0μg/100ml puff to 43.2μg/100ml puff (Trehy et al., 2011). In order assess the efficacy of e-cigarettes in converting nicotine from liquid to vapor, one group utilized a modified smoking machine to simulate puff behavior (Goniewicz, Kuma, Gawron, Knysak, & Kosmider, 2013). Testing 16 e-cigarettes brands and models, investigators found the efficacy and consistency of e-cigarettes to vaporize nicotine varied significantly both between and within brands and models. Moreover, all these studies reported e-cigarettes delivered lower levels of nicotine in comparison to tobacco cigarettes. However, a limitation of this work is smoking simulators do not fully simulate smoking behaviors.

Clinical findings to date suggest the type of device and user experience with e-cigarettes affect and alter patterns of use and subsequently, nicotine delivery. A crossover study aimed to evaluate subjective effects and nicotine delivery profiles from e-cigarettes. 16 e-cigarette naïve smokers were recruited to smoke own brand tobacco cigarettes, two models of 16mg nicotine e-cigarettes, and an unlit cigarette (Eissenberg, 2010) in bouts of 10 puffs. No significant increases in plasma nicotine concentration were found after using either e-cigarette devices. Similarly, a study employing the same methodological procedures reported e-cigarettes produced no significant increases in plasma nicotine concentrations in naïve e-cigarette users following two 10-puffs bouts (Vansickel et al., 2010). However, users reported reductions in tobacco withdrawal symptoms following e-cigarette use and e-cigarette craving reductions were greater than those following use of unlit cigarettes. However, e-cigarettes yielded lower plasma nicotine concentrations than nicotine inhalers and tobacco cigarettes. Another study investigated changes in serum nicotine concentrations in 9 e-cigarette naïve smokers randomized to smoke a tobacco cigarette, 16mg nicotine e-cigarette, or use a nicotine inhaler (C. Bullen et al., 2010). Tobacco cigarettes were found to produce peak nicotine concentrations faster and higher than e-cigarettes and inhalers. Moreover, the nicotine pharmacokinetic profile of the 16mg nicotine e-cigarettes was found comparable to that of nicotine inhalers. Similarly, a study of 20 e-cigarette naïve smokers reported significant increases in plasma nicotine concentrations after using 18mg nicotine e-cigarettes (Vansickel, Weaver, & Eissenberg, 2012). Consistent with previous findings, e-cigarette derived plasma nicotine concentrations remained below that of values obtained after smoking tobacco cigarettes. More recently, a study found 11mg nicotine e-cigarettes to produce serum cotinine levels comparable to that of tobacco
cigarettes after active smoking by e-cigarette naïve smokers (Flouris et al., 2013). These studies suggest e-cigarette nicotine delivery to be modest in new or inexperienced users.

Conversely, studies with experienced e-cigarette users have reported significant increases in nicotine and cotinine levels. A mail-out study involving 31 daily e-cigarette users found significant levels of cotinine in saliva samples (Etter & Bullen, 2011b). Of the 31 participants, 30 reported no tobacco product or NRT use within the past 48 hours and mean saliva cotinine levels were 322ng/ml. This is comparable to that of tobacco cigarette smokers (Wall, Johnson, Jacob, & Benowitz, 1988) and higher than that of NRT users (Benowitz, Zevin, & Jacob, 1997). Another study investigating the nicotine delivery profiles in experienced users using their preferred brand found e-cigarettes to significantly increase plasma nicotine concentrations and heart rate within 5 minutes of the first puff (Vansickel & Eissenberg, 2013). After ad libitum smoking for one hour, plasma nicotine levels were 16.3ng/ml. Similarly, significant increases in plasma nicotine concentrations were observed in 14 regular e-cigarette users after both smoking a 10-puff bout and smoking ad libitum for one hour (Dawkins & Corcoran, 2013). Plasma nicotine following ad libitum smoking reached a mean concentration of 13.91ng/ml. Previous studies have found plasma nicotine concentrations from smoking a single tobacco cigarette to range from 15ng/ml to 20ng/ml (Benowitz, Jacob, & Herrera, 2006). Therefore studies in e-cigarette users suggest experience may affect nicotine delivery and experienced e-cigarette users may achieve and maintain significant concentrations of plasma nicotine.

Moreover, the effectiveness of nicotine delivery by e-cigarettes is associated with many factors including the type and generation of devices used (Farsalinos et al., 2014). Newer generations of devices with higher battery voltages resulted in higher plasma nicotine concentrations. Moreover, e-cigarettes containing high doses of nicotine have been found to aid in achieving and maintaining smoking abstinence in experienced daily e-cigarette users (Farsalinos, Romagna, et al., 2013a). Nonetheless, e-cigarettes simulate the motions and behavioral pattern of smoking tobacco cigarettes that contribute to tobacco dependence (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005). As such, despite the inconsistencies in nicotine delivery, e-cigarettes may reduce craving, nicotine withdrawal symptoms, and tobacco cigarette consumption by satisfying the behavioral component of addiction (Christopher Bullen et al., 2013; Caponnetto et al., 2013; Polosa et al., 2011). However, the efficacy of e-cigarettes as smoking cessation aids remains unclear.

1.5.10.4. Smiling Topography

As discussed in the previous section, nicotine delivery from e-cigarettes may vary and improve with experience. However, while studies have suggested there to be a learning curve (Hajek et al., 2015), it is unclear how users increase nicotine intake.

A preliminary online survey of 3587 participants reported e-cigarette users took 120 puffs daily (Etter & Bullen, 2011a). Another study quantified e-cigarette puff and exhalation durations seen in Youtube
videos and reported significantly longer puff durations for e-cigarette users in comparison to tobacco cigarette smokers (Hua et al., 2013). Investigators postulated that longer puff durations compensated for lower nicotine delivery from e-cigarettes. However, the study was severely limited by lack of controls, and user demographic and e-cigarette information.

In a crossover study, 45 experienced e-cigarette users and 35 tobacco cigarette smokers were video recorded while smoking (Farsalinos, Romagna, et al., 2013b). E-cigarette users smoked e-cigarettes while tobacco cigarette smokers attended two visits and smoked both e-cigarettes and tobacco cigarettes. Significant differences were observed between smoking topography of e-cigarettes and tobacco cigarettes. Moreover, experienced e-cigarette users were found to take significantly longer puffs and use devices more intensively than e-cigarette naïve users.

More recently, a study recruited 20 e-cigarette naïve smokers to substitute use of regular tobacco cigarettes with e-cigarettes for two weeks (Lee, Gawron, & Goniewicz, 2015). Participants attended 3 study visits during which they were instructed to smoke ad libitum with a puff topography monitor was connected to the e-cigarettes. Between the initial visit and the first week of e-cigarette use, the mean puff duration increased significantly while the flow rate decreased. As such, topography studies suggest the mean puff duration of e-cigarettes to be significantly longer than that of tobacco cigarettes.

1.5.10.5. Clinical Trials of E-Cigarettes for Smoking Cessation

Few clinical smoking cessation trials of e-cigarettes have been conducted to date. Bullen et al conducted a 6-month randomized control study wherein 657 smokers motivated to quit smoking were randomized to be mailed 16mg nicotine e-cigarettes, 0mg nicotine e-cigarettes, and 21mg nicotine patches (Christopher Bullen et al., 2013). Investigators found rates of smoking abstinence were comparable between nicotine patches and e-cigarettes regardless of nicotine content. However, due to unexpectedly small differences in the rates of abstinence, the study was insufficiently powered to detect significant differences in abstinence between the treatment groups. Similarly, Caponnetto et al conducted a 12-month prospective randomized control study investigating smoking reduction and cessation in smokers with no intention to quit (Caponnetto et al., 2013). Investigators randomized 300 smokers to use e-cigarettes with varying nicotine doses or no-nicotine e-cigarettes for 12 weeks and found significant reductions in cigarette consumption per day regardless of e-cigarette nicotine content. Both studies suggest e-cigarettes to be potential smoking cessation aids; however further research is required to better understand the influence of nicotine delivery on the efficacy of e-cigarettes as smoking cessation aid. Adriaens et al conducted a randomized clinical trial wherein 48 participants with no intention to quit smoking were randomized into two experimental e-cigarette groups and one control tobacco cigarette group (Adriaens et al., 2014). Second-generation e-cigarettes were used in this clinical trial as they have previously been found to delivery nicotine more effectively than first-generation e-cigarettes. E-cigarettes were found to produce levels of cigarette craving reduction comparable to that from smoking tobacco cigarettes. Moreover, e-
cigarettes were reported to decrease the number of cigarettes smoked per day and increase tobacco cigarettes smoking abstinence.

In order to investigate whether e-cigarettes may be more effective than NRT as a smoking cessation aid for individuals with mental illness, a secondary analysis of the Bullen et al trial was conducted (O'Brien, Knight-West, Walker, Parag, & Bullen, 2015). Eighty-six of the 657 participants enrolled reported using at least one medication associated with mental illness. At 6-months, no significant differences in quit rates were observed between participants with and without mental illnesses. While rates of relapse were significantly higher in participants with mental illness, it was consistent between treatment groups. Moreover, at 6-months, participants with mental illnesses randomized to use 16mg nicotine e-cigarettes smoked significantly fewer cigarettes than those allocated to use 21mg nicotine patches and 0mg nicotine e-cigarettes. As a result, investigators suggested e-cigarettes may be effective as smoking cessation or harm reduction aids for smokers with mental illness.

1.5.10.6. Abuse Liability and Safety

As e-cigarettes gain in popularity, their abuse liability is a primary concern. Abuse liability often defined as the potential of a substance to be used for non-medical purposes that may lead to dependence (FDA, 2010). As previously mentioned, the pharmacokinetics, the pharmacodynamics, reinforcing effects, and adverse effects of nicotine all contribute to the abuse liability of tobacco products (L. P. Carter et al., 2009).

A study investigated nicotine dependence in 111 e-cigarette users who had completely substituted tobacco smoking with e-cigarette use for at least one month (Farsalinos, Romagna, et al., 2013a). When asked to score their previous and current dependence on tobacco cigarettes and e-cigarettes on a visual analogue scale (VAS), the mean score was 59 for e-cigarette dependence and 83 for tobacco cigarette dependence. However, only one question was asked regarding dependence and tobacco cigarette dependence was assessed retrospectively.

To assess the abuse liability of e-cigarettes, a study recruited 20 e-cigarette naïve tobacco cigarette smokers (Vansickel et al., 2012). Following an e-cigarette sampler session, factors associated with abuse liability were assessed using the multiple choice procedure (MCP). Participants chose to receive 10 puffs from e-cigarette over a mean $1.06 or three puffs from own brand tobacco cigarettes. In contrast, participants chose to receive 10 puffs from own brand tobacco cigarettes over a mean $1.50. These results suggest that e-cigarettes have a lower abuse potential than tobacco cigarettes. However, the study included only e-cigarette naïve users and choices were made between familiar own brand tobacco cigarettes and unfamiliar novel e-cigarettes.

Since e-cigarettes do not burn tobacco, the quantity of harmful compounds delivered during use has been suggested to be significantly lower than that from tobacco cigarettes (Goniewicz, Knysak, et al.,
However, one early study investigating chemical composition of e-cigarette aerosols found trace amounts of formaldehyde and acetaldehyde (Laugesen, 2008). Similarly, in analysis of 18 e-cigarette products, diethylene glycol was detected in one sample of e-cigarette liquid though levels detected were not disclosed (Westenberger, 2009).

Clinical studies of e-cigarette safety since then have found exposure to toxic substance from e-cigarettes to be significantly lower than that from tobacco cigarettes. To investigate volatile organic compounds (VOC), tobacco-specific nitrosamines (TSNA), carbonyl compounds, and metals emitted from e-cigarettes, a study produced vapor from 12 brands of e-cigarettes and a nicotine inhaler using a smoking simulator (Goniewicz, Knysak, et al., 2013). While formaldehyde, acetaldehyde, acrolein, and various TSNAs were identified in the emitted vapors, levels detected were 9 to 450 times lower than those emitted from tobacco cigarettes and were often comparable to amounts emitted from the nicotine inhaler. Another study evaluated levels of tobacco-specific nitrosamines (TSNAs) in 105 e-cigarette liquids from 11 companies and a mean TSNA level of 12.99μg/L was detected (Kim & Shin, 2013), an amount comparable to exposure from NRT use and significantly lower than from tobacco cigarettes. More recently, a study investigating 159 e-cigarette liquids from 36 manufactures found levels of diacetyl and acetyl propionyl in e-cigarette liquid and vapor to be 10 to 100-fold lower than those observed from smoking tobacco cigarettes (Farsalinos, Kistler, Gillman, & Voudris, 2015).

Moreover, studies have reported the level of cellular toxicity to be significantly lower than that of tobacco cigarette smoke. Studies in fibroblast cells (Romagna et al., 2013) and myocardial cells (Farsalinos, Romagna, Allifranchini, et al., 2013) have found e-cigarette vapor and liquid to be moderately cytotoxic. However, the level of toxicity was found to be significantly lower than that of tobacco cigarette smoke in both studies.

A study assessing effects of passive e-cigarette vapor exposure found no significant amounts of carbon monoxide (CO) and volatile organic compounds (VOCs) were emitted from e-cigarettes (Czogala et al., 2014). Moreover, while substantial amounts of nicotine were emitted from e-cigarettes, levels were significantly lower than those emitted from tobacco cigarettes.

As a result, substitution of tobacco cigarettes for e-cigarettes may significantly reduce exposure to toxic compounds and e-cigarettes may act as a harm reduction strategy. However, few studies have investigated the association between e-cigarette use and cigarette craving reduction.

Nicotine conditioned stimuli may contribute to cigarette craving and withdrawal symptoms, as well as motivating drug use. E-cigarettes may uniquely satiate behavioral cues by simulated smoking behavior and clinical trials to date have suggested e-cigarettes to be effective smoking cessation or harm reduction aids. However, further research is required to better understand underlying mechanisms, namely the efficacy of e-cigarettes, with or without nicotine delivery, to alleviate cigarette craving.
2. Methods

2.1. Study Design

This was a Latin-Square randomized, single-blind, within-subject study investigating the efficacy of non-nicotinic e-cigarettes in reducing cue- and withdrawal-induced cravings in daily dependent smokers. Secondary outcome measures included changes in mood, smoking topography, expired carbon monoxide, and physiological effects such as heart rate and blood pressure. A total of 41 participants completed the study. Smoking craving was assessed using standardized questionnaires under four distinct experimental conditions: (1) smoking tobacco cigarettes; (2) using no-nicotine e-cigarettes with placebo lozenges; (3) using no-nicotine e-cigarettes with nicotine lozenges (4mg); (4) using nicotine lozenges alone (4mg).

The study consisted of four visits to the Centre for Addiction and Mental Health (CAMH), each lasting four hours. Eligibility screenings were first conducted over a phone call. Eligible participants were scheduled to attend their first study visit, during which informed consent was collected and participants were randomized to one of four treatment groups. The study design is summarized in Table 2.1 below. All participants received all four experimental conditions. However, the order in which experimental conditions were administered varied between groups to account for order effects. During e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges visits, participants were not aware that the e-cigarettes contained no nicotine. Similarly, participants were blinded to whether the lozenges contained nicotine or not. Participants were given the option to schedule each of the four study visits whenever they are available so long as visits did not occur on consecutive days and participants attended all four study visits within three months.

This study was approved by the CAMH Research Ethics Board and was conducted in accordance with the Declaration of Helsinki. The study was registered as a clinical trial on www.clinicaltrials.gov (Identifier: NCT02108626).
Table 2.1: Partial Latin Square of Experimental Conditions. Each participant attended all four study visits. At enrollment, participants were randomized into Group A, B, C, or D. All participants underwent all four experimental conditions (smoking tobacco cigarettes, e-cigarettes with placebo lozenges, e-cigarettes with nicotine lozenges, and using nicotine lozenges alone); however, the order in which conditions were administered varied between groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Tobacco Cigarette</td>
<td>E-Cigarette with Placebo Lozenge</td>
<td>E-Cigarette with Nicotine Lozenge</td>
<td>Nicotine Lozenge</td>
</tr>
<tr>
<td>B</td>
<td>E-Cigarette with Nicotine Lozenge</td>
<td>Tobacco Cigarette</td>
<td>Nicotine Lozenge</td>
<td>E-Cigarette with Placebo Lozenge</td>
</tr>
<tr>
<td>C</td>
<td>E-Cigarette with Placebo Lozenge</td>
<td>Nicotine Lozenge</td>
<td>Tobacco Cigarette</td>
<td>E-Cigarette with Nicotine Lozenge</td>
</tr>
<tr>
<td>D</td>
<td>Nicotine Lozenge</td>
<td>E-Cigarette with Nicotine Lozenge</td>
<td>E-Cigarette with Placebo Lozenge</td>
<td>Tobacco Cigarette</td>
</tr>
</tbody>
</table>

2.2. Eligibility Screening

Participants were eligible if they (1) were between ages 18 and 65; (2) scored 3 or higher on the Fagerstrom Test of Nicotine Dependence (FTND); (3) smoked at least 10 cigarettes per day; (4) had never used an e-cigarette prior to the study; (5) had no intention to quit smoking within the next three months; (6) were able to provide written informed consent (see Appendix 1); (7) were willing to attend four scheduled study visits at CAMH.

Participants were excluded if they (1) had medical or psychiatric problems requiring treatment; (2) were pregnant or lactating women. Medical and psychiatric problems and pregnancy were determined through self-report only.

2.3. Participant Recruitment

Participants were recruited from placing advertisements on online classified websites (www.kijiji.ca and www.toronto.craigslist.ca) and local community message boards in the downtown Toronto area (see Appendix 2 for advertisements). All individuals were asked for verbal consent to conduct the phone eligibility screening.

2.4. Sample Size Calculations

A priori sample size calculation was conducted using results from (Dawkins, Turner, Hasna, & Soar, 2012). A sample size of 40, 10 in each of the four groups, was found sufficient to provide 80% power to detect a significant difference with an alpha value of 0.05.
2.5. **Study Procedures**

2.5.1. **Pre-Visit Procedures**

Following a telephone screening (see Appendix 3), eligible individuals were scheduled to attend their first study visit. Confirmation emails, containing study visit preparation guidelines, were sent to participants the same day as the phone screening if possible. Participants also received phone call reminders on the day prior to their scheduled study visit, during which they were also reminded to abstain from eating, drinking anything except water, and smoking for 12 hours prior to the beginning of their study visits.

2.5.2. **Visit Day Procedures**

During the first study visit, informed consent was obtained before proceeding with visit procedures. Study procedures, risks and benefits, and confidentiality were thoroughly discussed with participants. Participants were then provided a copy of the signed consent form for future reference.

Participants were asked to attend study visits at CAMH at 9:00AM. Upon arrival to each study visit, participants were provided a standard breakfast. Expired alcohol and carbon monoxide (CO) measurements were taken to confirm overnight abstinence from alcohol and smoking. Expired carbon monoxide was measured using a piCO+ smokerlyzer (Bedfont Scientific Ltd) and was required to be less than 10 parts per million (ppm). Breath alcohol was assessed by a Drivesafe™ Breath Alcohol Tester (ACS Corp) and was required to be 0.000 mg/dL. If measurements exceeded the respective levels, participants were rescheduled to attend the study visit on another day.

Baseline physiological measurements such as heart rate and blood pressure were collected. Participants were then asked to complete the Brief Questionnaire of Smoking Urges (QSU-Brief), Positive and Negative Affect Scale (PANAS), and Visual Analogue Scale (VAS) to measure baseline levels of craving and mood. Additional baseline assessments conducted during the first visit included demographics, history of smoking and tobacco product use, FTND, and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). These instruments are described in detail below.

Following all baseline assessments, participants were given five minutes to use whichever experimental condition had been assigned. During the tobacco cigarette condition visits, participants were escorted to a negative pressure smoking room in the Biobehavioral Addictions and Concurrent Disorders Laboratory (BACDRL) at CAMH and allowed to smoke ad lib for five minutes. After the five minute smoking condition, participants were escorted back to the study visit room to attend the remainder of the visit.

During the e-cigarette condition visits, participants were provided a SmokeNV Canadian Premium Disposable e-cigarette (see Appendix 6) to use concurrently with either a nicotine lozenge or a placebo lozenge. Participants were informed that the e-cigarettes and lozenges may or may not contain nicotine. Similarly, during the lozenge alone condition visits, participants were provided nicotine lozenges, but
were blinded to whether the lozenges contained nicotine. A camera was set up in the corner of the study room to record the administration sessions for analysis of smoking topography. Participants were then asked to remain in a lounge area adjacent to the study room.

One hour after the 5-minute experimental condition, the cue paradigm (described in detail in Section 2.8) was administered. Participants were first presented with a set of neutral visual and tactile cues, followed by a set of smoking-related cues. Specifically, during the neutral cue presentation, participants viewed a 5-minute slideshow of neutral images, such as pots and calculators, while holding a pen. Conversely, during the smoking cue presentation, participants viewed a 5-minute slideshow of smoking-related images, such as lit cigarettes and ash trays, while holding an unlit tobacco cigarette. Thirty images were included in each presentation, and each slide lasted ten seconds long and slides were randomized prior to each presentation. VAS, PANAS, and QSU-Brief were completed following each set of cues. The cue paradigm was repeated again two hours later (three hours after the experimental condition) and the same questionnaires were completed after each set of cues as outlined in Figure 2.1.

At the end of each study visit, physiological measurements such as expired CO, heart rate, and blood pressure, were assessed again. A 49-item symptoms checklist was completed to assess adverse events participants experienced during the study visit. Participants were then compensated and scheduled to attend their next visit. All participants received $30.00CAD after completing the first study visit, $50.00CAD after the second visit, $70.00CAD after the third visit, and $90.00CAD after the fourth and final visit, for a total of $240.00CAD. Participants were also compensated with two transit fares (TTC tokens) after completing each visit for transportation to and from CAMH.

<table>
<thead>
<tr>
<th>9:00 AM</th>
<th>9:30 AM</th>
<th>10:30 AM 1 hour post-condition</th>
<th>12:30 PM 3 hours post-condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival</td>
<td>Breath Alcohol Test *</td>
<td>Neutral Cues Questionnaires</td>
<td>Neutral Cues Questionnaires</td>
</tr>
<tr>
<td>Informed consent *</td>
<td>Expired CO</td>
<td>Smoking Cues Questionnaires (Cue-induced craving)</td>
<td>(Withdrawal-induced craving)</td>
</tr>
<tr>
<td></td>
<td>Standard Breakfast</td>
<td></td>
<td>Smoking Cues Questionnaires (Cue- and withdrawal-induced craving)</td>
</tr>
<tr>
<td></td>
<td>Vitals - Heart Rate - Blood Pressure</td>
<td></td>
<td>Adverse Symptoms Checklist</td>
</tr>
<tr>
<td></td>
<td>Questionnaires - QSU-Brief - PANAS - VAS</td>
<td></td>
<td>Vitals</td>
</tr>
<tr>
<td></td>
<td>Experimental Condition (5-min exposure)</td>
<td></td>
<td>Expired CO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Compensation</td>
</tr>
</tbody>
</table>

**Figure 2.1:** Study day procedures. Participants completed craving and mood assessments at five time points: (1) baseline measurements taken upon arrival; (2) following neutral-cues presentation one hour after the experimental condition; (3) following smoking-cues presentation one hour after the experimental; (4) following neutral-cues presentation three hours after the experimental condition; (5) following smoking-cues presentation three hours after the experimental. Procedures marked with (*) are conducted only during participants' first study visits.
2.5.3. **Cue Presentation Procedures**

2.5.3.1. **Neutral Cues**

Participants were seated alone in the study room, without any smoking cues, and presented a slideshow on a laptop of neutral cues along with a box of pens. The neutral cue slideshow consisted of thirty images set to a ten second automatic timer and lasted a total of five minutes. Faces of people and various objects such as plants, pots, calculators, and brushes were among the images presented (see Appendix 4 for a sample of cues). In addition to watching the slideshow, participants were instructed to pick up and hold a pen. The QSU-Brief, PANAS, and VAS were completed after the cue presentation as previously described.

2.5.3.2. **Smoking Cues**

Similar to the neutral cues, smoking cues consisted of a visual and tactile component. The smoking cue slideshow consisted of thirty images set to a ten second timer and lasted a total of five minutes. Images included cigarettes, lighters, ashtrays, and various people lighting and smoking cigarettes (see Appendix 4 for a sample of cues). A pack of Belmont cigarettes were placed on the table and participants were instructed to hold a cigarette for the duration of the slideshow. Questionnaires assessing cigarette craving and mood were completed following the cue presentation.

Presentation of neutral cues preceded that of smoking cues to prevent carry-over effects.

2.6. **Materials**

2.6.1. **Nicotine Lozenges**

Nicotine polacrilex (Nicorette® and Life Brand) lozenges were purchased from local pharmacies (Shoppers Drug Mart). Due to stock shortages, the first 39 participants received Nicorette® mini nicotine lozenges (GlaxoSmithKline) while the remaining 4 participants received Life Brand mini nicotine lozenges (Perrigo).

During both ‘e-cigarette with nicotine lozenge’ and ‘nicotine lozenge alone’ visits, participants received 4mg nicotine doses administered in the form of two 2mg mini nicotine lozenges. Participants were instructed to place the lozenges in the oral vestibule (the area between the cheek and gums) to dissolve, one lozenge on each side of the mouth. During the ‘e-cigarette with nicotine lozenge’ visit, participants were instructed to place the lozenges in their mouths at the beginning of the 5-minute smoking periods and to use the non-nicotinic e-cigarettes concurrently. During ‘e-cigarette with placebo lozenge’ visits, participants were given identical instructions regarding medication use.
2.6.2. **Disposable Electronic Cigarettes**

SmokeNV Canadian Premium disposable e-cigarettes were purchased directly from SmokeNV. E-cigarette liquid contained food-grade vegetable glycerin and artificial tobacco flavoring. One pack of e-cigarettes contained two e-cigarettes, and pack was assigned to each participant. During each of the ‘e-cigarette with placebo lozenge’ and ‘e-cigarette with nicotine lozenge’ visits, participants received one brand new e-cigarette from their assigned packed to use for the 5-minute smoking period. Following the smoking periods, the e-cigarettes were collected, marked as used, and replaced in the pack for storage and record keeping (see Appendix 6).

2.7. **Smoking Topography**

A Canon camera was installed on a tripod and set up in the corner of the study room. The camera began recording video shortly prior to participants’ 5-minute smoking periods during visits in which tobacco cigarettes or e-cigarettes were the assigned conditions. Video recording ended following the smoking period. Videos were analyzed for puff number, puff duration, and interpuff interval (IPI) data. Frame-by-frame analysis was conducted for timing measurements. Puff duration was the time interval between the frames during which the mouth was closed and opened to release the cigarette. Interpuff interval was the time interval between the frames during which the mouth opened to release the cigarette and closed to take the next puff. The number of puffs taken was counted beginning from the first puff until 5 minutes later from that time.

2.8. **Physiological Measures**

2.8.1. **Carbon Monoxide (CO) Breathalyzer**

Smoking abstinence was confirmed by measuring breath carbon monoxide (CO) levels using a smokerlyzer (piCO® Smokerlyzer, Bedfont Scientific Ltd, Kent, England). Participants were required to have a CO level of 10 ppm or less to proceed with the study visit. If measures were higher than 10 ppm, participants were sent home and study visits were rescheduled.

2.8.2. **Heart Rate and Blood Pressure**

Heart rate was measured manually by pulse counting for 30 seconds and values were multiplied by 2 to represent the number of beats per minute. Blood pressure was measured using a mobile sphygmomanometer (Welch Allyn®, USA) fitted with a Size-11 Adult blood pressure cuff.

2.9. **Self-Report Measures**

The Fagerström Test of Nicotine Dependence (FTND), WHO Disability Assessment Schedule 2.0 (WHODAS 2.0), Brief Questionnaire of Smoking Urges (QSU-Brief), Positive and Negative Affect Scale (PANAS), and Visual Analogue Scale (VAS) were administered during study visits. These measures are
described in more detail below. The Fagerström Test of Nicotine Dependence and WHO Disability Assessment Schedule 2.0 were administered only during the first study visit. Subjective cigarette cravings were assessed with the Brief Questionnaire of Smoking Urges and the Visual Analogue Scale. Along with the Positive and Negative Affect Scale, the Visual Analogue Scale also measured changes in mood.

Adverse events experienced during the study visit were reported verbally and recorded to participant files, and by completing an items checklist.

2.9.1. **Fagerström Test of Nicotine Dependence (FTND)**

The Fagerström Test of Nicotine Dependence (FTND) is a 6-item used to establish and quantify nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) derived from the original 8-item Fagerström Tolerance Questionnaire (FTQ) (Fagerström, 1978). While the FTND has been found to have lower internal reliability (Etter, 2005) than other measures of nicotine dependence such as the Minnesota Nicotine Withdrawal Scale (MNWS) (Etter & Hughes, 2006) and Questionnaire of Smoking Urges (QSU) (Tiffany & Drobes, 1991), a recent study found the FTND to have similar internal consistencies as the other measures (Weinberger et al., 2007). Moreover, the FTND has been found to have high test-retest reliability.

2.9.2. **Brief Questionnaire of Smoking Urges (QSU-Brief)**

The Questionnaire of Smoking Urges (QSU) is a 32-item self-report instrument measuring four distinct aspects of smoking urges including desire to smoke, anticipation of immediate positive outcome from smoking, anticipation of immediate relief from nicotine withdrawal, and intention to smoke (Tiffany & Drobes, 1991). The questionnaire evaluates two factors. The first factor addresses both the desire and intention to smoke with anticipation of pleasure from smoking while the second factor investigated relief from nicotine withdrawal with a desire to smoke. Since cravings and smoking urges were assessed at five time points during each study visit, the study utilized a shortened form of the original QSU, the Brief Questionnaire of Smoking Urges (QSU-Brief).

The QSU-Brief is a 10-item self-report instrument (Cox, Tiffany, & Christen, 2001). The five most robust items from each factor of the original QSU was included to more efficiently evaluate the factors. Similar to the original QSU, the QSU-Brief uses a 7-point Likert scale, scores ranging from 1 (strongly disagree) to 7 (strongly agree), to indicate how strongly participants agreed or disagreed with a question.
2.9.3. **Positive and Negative Affect Scale (PANAS)**

The Positive and Negative Affect Scale (PANAS) is a 20-item self-report questionnaire estimating two independent factors of emotion, positive and negative affect (Watson, Clark, & Tellegen, 1988). Each of the ten items aims to measure the intensity of a specific feeling or emotion experienced by participants during a given timeframe. A 5-point Likert scale with scores ranging from 1 (slightly or not at all) to 5 (extremely) is used to rate each item.

2.9.4. **Visual Analogue Scale (VAS)**

A Visual Analogue Scale (VAS) a self-report instrument used to obtain unbiased scores of psychological and behavioral characteristics (Folstein & Luria, 1973). The scale often consists of a line anchored by two limits representing the extremes of a question and participants are asked to mark a point on the line corresponding to the intensity of the feeling mentioned in the question.

In the present study, the complete VAS consisted of 29 items to investigate mood and craving. Five items measuring craving were “I have a desire for cigarettes right now”, “If possible, I would smoke a cigarette right now”, “All I want right now is a cigarette”, “I have an urge for cigarettes”, and “I crave cigarettes right now”. Twenty-five VAS items assessing mood included “Calm”, “Stressed”, and “Frustrated”. Participants were asked to indicate on scale of 1 to 100 how intensely the items were felt or applied to them at the moment.

2.9.5. **WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)**

The World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) is a standardized cross-cultural measurement of health status, functioning, and disability (Ustün et al., 2010) linked to the International Classification of Functioning, Disability, and Health (ICF). The WHODAS 2.0 evaluates the level of functioning in six major life domains including cognition (understanding and communication), mobility (moving and getting around), self-care (ability to attend to personal hygiene, dressing and eating, and living alone), getting along (ability to interact with others), life activities (ability to carry out responsibilities), and participation in society (ability to engage in community and recreational activities). Several versions of the WHODAS are currently available including a 12-item and a 36-item version. The WHODAS 2.0 may also be self-administered, completed through an interview, or completed by a proxy.

The current study utilized the 36-item self-administered WHODAS 2.0. A scale from 0 (None) to 4 (Extreme and cannot do) was used to rate each item. Percentages were calculated for each domain and the overall WHODAS 2.0
2.10. **Adverse Effects**

Adverse events reported verbally by participants throughout study visits were reported in participant files. At the end of each visit, participants also completed at 49-item symptoms checklist (see Appendix 5).

2.11. **Ethical Considerations**

The initial study protocol was submitted to the CAMH Research Ethics Board in January 2014 and approved in March 2014. All participants provided written informed consent prior to enrollment and participation in this study. Participant numbers were assigned to all participant and all data collected during the study was stored on a FIPS Level 3 encrypted USB and/or stored in a locked cabinet at all times. The study was registered with ClinicalTrials.gov (Identifier: NCT02108626).

2.12. **Data Analyses**

Subject demographics were analyzed using one-way ANOVA to assess for differences between groups. Smoking topography, smoking trends, QSU-Brief, VAS, and PANAS data were first analyzed for outliers and normality. Since the sample size was less than 50, the Shapiro-Wilk Test of Normality was used to determine if the data were normally distributed (p > 0.05).

The QSU-Brief, VAS, and PANAS data were analyzed using repeated measures ANOVA with condition (tobacco cigarettes, e-cigarettes with nicotine lozenges, e-cigarettes with placebo lozenges, and nicotine lozenges alone) and time (post-neutral cues presented one hour after conditions, post-smoking cues presented one hour after conditions, post-neutral cues presented three hours after conditions, and post-smoking cues presented three hours after conditions) as within-subject factors and group (A, B, C, D) as a between-subject factor. During analysis of gender differences, gender (female, male) was used as a between-subject factor. Mauchly’s Test of Sphericity was used to assess for equality of within-subject factor variances (p > 0.05). If the assumption of sphericity was not met, corrections were made using epsilon (ε) values calculated either by the Greenhouse-Geisser or Huynh-Feldt method. If the estimated epsilon (ε) value was less than 0.75, the Greenhouse-Geisser correction was used. Conversely, if the epsilon (ε) value was greater than 0.75, the Huynh-Feldt correction was used. When significant differences were detected, post-hoc pairwise comparisons were conducted with a Bonferroni adjustment to account for multiple comparisons.

Cue-induced cravings were assessed by subtracting QSU-Brief and VAS scores reported post-smoking cues one hour after conditions with those reported post-neutral cues one hour after conditions. Withdrawal-induced cravings were assessed by subtracting scores reported post-neutral cues three hours after conditions with those reported post-neutral cues one hour after conditions. Cravings by the end of visit were assessed by subtracting scores reported post-smoking cues three hours after conditions with those post-neutral cues one hour after conditions. Repeated measures ANOVA was
conducted with condition and craving (cue-induced, withdrawal-induced, and end-of-visit) as within-subject factors and group as a between-subject factor. When significant differences were detected, post-hoc comparisons were conducted with a Bonferroni adjustment to account for multiple comparisons.

Physiological assessments (carbon monoxide levels, heart rate, and blood pressure) were analyzed using paired sample t-tests with condition and time (start-of-visit and end-of-visit) as within-subject factors.

Smoking topography (number of puffs taken, puff duration, interpuff interval) was analyzed using non-parametric Friedman test with condition (tobacco cigarettes, first e-cigarette, and second e-cigarettes; or tobacco cigarette, e-cigarettes with placebo lozenges, e-cigarettes with nicotine lozenges) as a within-subject factor. Post hoc pairwise comparisons were conducted with a Bonferroni correction for multiple comparisons. Smoking trends were analyzed with a two-way repeated measures ANOVA with condition and time (1-minute, 2-minute, 3-minute, 4-minute, 5-minute) as within-subject factors. Post-hoc comparisons were conducted with a Bonferroni adjustment to account for multiple comparisons.
3. Results

3.1. Study Participants

A total of 41 participants completed the study. At baseline, participant demographic information included age, gender, ethnicity, employment status, education, gross household income, smoking history, and Fagerström Test of Nicotine Dependence (FTND) scores. No significant differences in the demographics of participants randomized into each of the four study groups were observed. A summary of participant characteristics can be seen in Table 3.1.

Table 3.1: Baseline participant demographics. No significant differences were observed between groups. Overall WHODAS scores are presented as percentages. Values are expressed as mean ± standard deviation (SD). P-values shown reflect comparisons between groups.

<table>
<thead>
<tr>
<th>Sample (n=41)</th>
<th>Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.20 ± 10.97</td>
<td>36.15 ± 11.21</td>
</tr>
<tr>
<td>% Female (M:F)</td>
<td>19:22</td>
<td>5:8</td>
</tr>
<tr>
<td>Employment Status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>8 (19.51)</td>
<td>3 (23.08)</td>
</tr>
<tr>
<td>Part Time</td>
<td>9 (21.95)</td>
<td>2 (15.38)</td>
</tr>
<tr>
<td>Self-Employed</td>
<td>6 (14.63)</td>
<td>3 (23.08)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>17 (41.47)</td>
<td>5 (38.46)</td>
</tr>
<tr>
<td>Retired</td>
<td>1 (2.44)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Currently a student (%)</td>
<td>6 (14.63)</td>
<td>2 (15.38)</td>
</tr>
<tr>
<td>Education of High School or less (%)</td>
<td>25 (60.98)</td>
<td>8 (61.54)</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>29 (70.73)</td>
<td>10 (76.92)</td>
</tr>
<tr>
<td>Age smoked first whole cigarette</td>
<td>15.05 ± 3.05</td>
<td>15.15 ± 2.67</td>
</tr>
<tr>
<td>Age smoked cigarettes occasionally</td>
<td>15.85 ± 3.14</td>
<td>15.77 ± 3.11</td>
</tr>
<tr>
<td>Age started smoking daily</td>
<td>17.61 ± 3.46</td>
<td>18.54 ± 3.50</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>19.68 ± 8.15</td>
<td>20.23 ± 8.83</td>
</tr>
<tr>
<td>FTND score</td>
<td>6.39 ± 2.00</td>
<td>5.77 ± 2.05</td>
</tr>
<tr>
<td>WHODAS score</td>
<td>10.64 ± 15.36</td>
<td>--</td>
</tr>
</tbody>
</table>
As outlined in the participant recruitment flowchart (Figure 3.1), 147 individuals responded to the study recruitment ads. 15 people could not be contacted for the phone screening and 13 people declined phone screening. Of the 119 individuals who completed the phone screening, 51 were eligible for participation and scheduled to attend their first study visit. All ineligible individuals were referred to the Nicotine Dependence Clinic at CAMH. Of the 8 individuals who did not attend their first study visit, 4 withdrew from the study and 4 could not be reached. A total of 43 participants enrolled in the study and were randomized. However, one participant dropped out due to time conflicts with a new job while another became disinterested in completing the study and could not be contacted. As a result, 41 participants attended all four visits and completed the full study.

![Flowchart](image-url)  

**Figure 3.1**: Study flowchart. 147 individuals responded to study advertisements and 119 individuals underwent phone eligibility screening. Of the 51 individuals found eligible, 43 participants were enrolled and 41 participants completed the current study. All individuals who were ineligible, declined screening, or withdrew from the study were referred to the Nicotine Dependence Clinic at CAMH.
3.2. Smoking Topography

3.2.1. Order Effects

To investigate potential order effects, the smoking topography data was categorized by visit order for analysis. The visits during which participants smoked tobacco cigarettes were marked as “tobacco cigarette” visits; however, visits during which participants used e-cigarettes were marked depending on their order regardless of whether they were used concurrently with placebo or nicotine lozenges.

Outliers were found in the data regarding the total number of puffs taken, the mean puff duration, and the mean interpuff interval (IPI) of the 5-minute smoking period from the first and second visits during which participants used e-cigarettes. However, as the source of the outliers varied between e-cigarette visits, all data points were kept for analysis. Moreover, the data was not normally distributed. As a result, the non-parametric Friedman test was used to investigate differences in total puff number, mean puff duration, and mean interpuff interval between the two e-cigarette visits.

Significant differences in the total number of puffs taken were found between the three smoking visits, \( \chi^2(2) = 30.447, p < 0.0005 \). The total numbers of puffs taken during the 5-minute smoking period at each smoking visit is summarized in Table 3.2. A total of 18.90 ± 5.53 puffs were taken while using e-cigarettes with placebo lozenges and 21.27 ± 7.35 puffs were taken while using e-cigarettes with nicotine lozenges. A pairwise comparison with a Bonferroni correction for multiple comparisons found a statistically significant difference between the numbers of puff number taken during the first and second visits during which participants used e-cigarettes \( (p = 0.024) \).

Similarly, significant differences in the mean interpuff interval were observed between the smoking visits, \( \chi^2(2) = 32.049, p < 0.0005 \). The mean interpuff interval during the first e-cigarette visit was 14.94 ± 4.67 s while that of the second e-cigarette visit was 12.34 ± 4.85 s and a statistically significant difference was observed \( (p = 0.003) \).

The mean puff duration of the smoking visits were also found to be significantly different, \( \chi^2(2) = 37.706, p < 0.0005 \). The mean puff duration during the first e-cigarette visit was 2.80 ± 0.96 s while that of the second e-cigarette visit was 2.93 ± 1.13 s. However, pairwise comparisons with a Bonferroni correction found no significant difference between the two e-cigarette visits \( (p = 1.000) \).
Table 3.2: Smoking topography by e-cigarette use order. In comparison to the first e-cigarette visit, significantly more puffs were taken during the second e-cigarette visit. Mean IPI was significantly shorter during the second e-cigarette visit compared to the first e-cigarette visit. No significant difference in the mean puff duration was observed between e-cigarette visits. Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the Friedman test and p-values shown reflect post-hoc comparisons between the first and second e-cigarette visits.

<table>
<thead>
<tr>
<th></th>
<th>Visit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tobacco Cigarette</td>
<td></td>
</tr>
<tr>
<td>Number of Puffs (n)</td>
<td>14.32 ± 5.35</td>
<td></td>
</tr>
<tr>
<td>Mean Puff Duration (s)</td>
<td>1.71 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>Mean Interpuff Interval (s)</td>
<td>20.55 ± 8.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>First E-Cigarette</td>
<td></td>
</tr>
<tr>
<td>Number of Puffs (n)</td>
<td>18.90 ± 5.53</td>
<td>0.024</td>
</tr>
<tr>
<td>Mean Puff Duration (s)</td>
<td>2.80 ± 0.96</td>
<td></td>
</tr>
<tr>
<td>Mean Interpuff Interval (s)</td>
<td>14.94 ± 4.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second E-Cigarette</td>
<td></td>
</tr>
<tr>
<td>Number of Puffs (n)</td>
<td>21.27 ± 7.35</td>
<td></td>
</tr>
<tr>
<td>Mean Puff Duration (s)</td>
<td>2.93 ± 1.13</td>
<td>1.000</td>
</tr>
<tr>
<td>Mean Interpuff Interval (s)</td>
<td>12.34 ± 4.85</td>
<td>0.003</td>
</tr>
</tbody>
</table>

In order to further investigate differences in smoking behavior during the 5-minute periods, as well as potential order effects, the cumulative number of puffs taken up until each minute time point (1-minute, 2-minute, 3-minute, 4-minute, 5-minute) were tabulated. Mean cumulative number of puffs taken are presented in Table 3.3 and Figure 3.2.

Table 3.3: Cumulative number of puffs taken at various time points during the 5-minute smoking period, categorized by e-cigarette use order. In comparison to the first e-cigarette visit, significantly more puffs were taken cumulatively at each time point during the second e-cigarette visit. Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect post-hoc comparisons between the first and second e-cigarette visits.

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Cumulative Number of Puffs Taken (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tobacco Cigarette</td>
<td></td>
</tr>
<tr>
<td>1 Minute</td>
<td>4.12 ± 1.44</td>
<td>0.008</td>
</tr>
<tr>
<td>2 Minute</td>
<td>7.02 ± 2.43</td>
<td>0.011</td>
</tr>
<tr>
<td>3 Minute</td>
<td>9.90 ± 3.51</td>
<td>0.038</td>
</tr>
<tr>
<td>4 Minute</td>
<td>12.44 ± 4.46</td>
<td>0.053</td>
</tr>
<tr>
<td>5 Minute</td>
<td>14.32 ± 5.35</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>First E-Cigarette</td>
<td></td>
</tr>
<tr>
<td>1 Minute</td>
<td>4.88 ± 1.17</td>
<td></td>
</tr>
<tr>
<td>2 Minute</td>
<td>8.29 ± 2.12</td>
<td></td>
</tr>
<tr>
<td>3 Minute</td>
<td>12.02 ± 3.58</td>
<td></td>
</tr>
<tr>
<td>4 Minute</td>
<td>15.68 ± 4.83</td>
<td></td>
</tr>
<tr>
<td>5 Minute</td>
<td>18.90 ± 5.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second E-Cigarette</td>
<td></td>
</tr>
<tr>
<td>1 Minute</td>
<td>5.71 ± 1.87</td>
<td></td>
</tr>
<tr>
<td>2 Minute</td>
<td>9.78 ± 3.21</td>
<td></td>
</tr>
<tr>
<td>3 Minute</td>
<td>13.71 ± 4.58</td>
<td></td>
</tr>
<tr>
<td>4 Minute</td>
<td>17.66 ± 5.90</td>
<td></td>
</tr>
<tr>
<td>5 Minute</td>
<td>21.27 ± 7.35</td>
<td></td>
</tr>
</tbody>
</table>

A two-way repeated measures ANOVA was used to investigate the effect of various experimental conditions over time on the number of puffs taken. Mauchly’s Test of Sphericity found the assumption of sphericity was violated, $\chi^2(35) = 429.087$, $p < 0.0005$. Using an epsilon ($\epsilon$) value of 0.275, as calculated according to Greenhouse-Geisser, to correct the two-way repeated measure ANOVA, a statistically significant interaction was found between experimental conditions and time, $F(2.203, 88.134) = 12.780$, $p < 0.0005$, partial $\eta^2 = 0.242$. Therefore, simple main effects were investigated using repeated measures ANOVA.
An epsilon ($\epsilon$) value of 0.762, as calculated by Huynh-Feldt, was used to correct the repeated measures ANOVA. The number of puffs taken during the first minute of the smoking period was significantly different between smoking tobacco cigarettes (4.12 ± 1.44 puffs) and the first (4.88 ± 1.17 puffs) and second (5.71 ± 1.87 puffs) times using e-cigarettes, $F(1.523, 60.924) = 14.616, p < 0.0005$, partial $\eta^2 = 0.268$. Post hoc analysis revealed significant increases in the number of puffs taken while smoking tobacco cigarettes and the first (0.76 (95% CI, 0.17 to 1.34) puffs, $p = 0.007$) and second (1.59 (95% CI, 0.66 to 2.51) puffs, $p < 0.0005$) visits using e-cigarettes. A significant difference was also identified between the first and second e-cigarette visits, with a mean difference in puff number of 0.83 (95% CI, 0.18 to 1.48) puffs, $p = 0.008$).

Similarly, the cumulative number of puffs taken until the 2-minute time point was significantly different between experimental conditions ($F(1.662, 66.465) = 15.079, p < 0.0005$, partial $\eta^2 = 0.274$) using an epsilon ($\epsilon$) value of 0.831 was used to correct the repeated measures ANOVA. The number of puffs taken until the 2-minute mark during the tobacco cigarette condition was 7.02 ± 2.43 puffs, while that from using e-cigarettes for the first and second time were 8.29 ± 2.12 puffs and 9.78 ± 3.21 puffs respectively. Significant differences were found in the number of puffs taken while smoking tobacco cigarettes and the first visit using e-cigarettes, with a mean difference in puff number of 1.27 (95% CI, 0.29 to 2.25) puffs, $p = 0.008$. Significant differences were also observed between smoking tobacco cigarettes and the second visit using e-cigarettes (2.76 (95% CI, 1.24 to 4.28) puffs, $p < 0.0005$) as well as between the first and second e-cigarette visits (1.49 (95% CI, 0.28 to 2.69) puffs, $p = 0.011$).

At the 3-minute time point, 9.90 ± 3.51 puffs had been taken during the tobacco cigarette smoking visit while 12.02 ± 3.58 puffs and 13.71 ± 4.58 puffs had been taken during the first and second e-cigarette visits. Significant differences were found between the cumulative puff numbers from the conditions ($F(1.765, 70.604) = 14.118, p < 0.0005$, partial $\eta^2 = 0.261$) after corrections with an epsilon ($\epsilon$) value of 0.883. Significant differences were found in the number of puffs taken while smoking tobacco cigarettes and the first (2.12 (95% CI, 0.55 to 3.70) puffs, $p = 0.005$) and second (3.81 (95% CI, 1.67 to 5.94) puffs, $p < 0.0005$) e-cigarettes visits. A significant difference was also observed between the first and second e-cigarette visits, with a mean difference in puff number of 1.68 (95% CI, 0.07 to 3.30) puffs, $p = 0.038$).

The total number of puffs taken until the 4-minute time point were significantly different between the conditions ($F(1.761, 70.459) = 15.909, p < 0.0005$, partial $\eta^2 = 0.285$) after corrections with an epsilon ($\epsilon$) value of 0.881. Within the first 4 minutes of smoking, 12.44 ± 4.46 puffs had been taken on tobacco cigarettes while 15.68 ± 4.83 puffs and 17.66 ± 5.90 puffs had been taken when using e-cigarettes for the first and second time. Significant differences were found in the number of puffs taken while smoking tobacco cigarettes and the first (3.24 (95% CI, 1.09 to 5.40) puffs, $p = 0.002$) and second (5.22 (95% CI, 2.44 to 8.00) puffs, $p < 0.0005$) e-cigarettes visits.
Finally, significant differences were found in the cumulative puff numbers at the 5-minute time point (F(1.659, 66.374) = 18.346, p < 0.0005, partial $\eta^2 = 0.314$) after corrections with an epsilon ($\varepsilon$) value of 0.830. By the end of the smoking period, 14.32 ± 5.35 puffs had been taken from tobacco cigarettes while 18.90 ± 5.53 puffs and 21.27 ± 7.35 puffs had been taken from using e-cigarettes the first and second time. The number of puffs taken while smoking tobacco cigarettes was significant different from that of the first (4.59 (95% CI, 1.95 to 7.23) puffs, p < 0.0005) and second (6.95 (95% CI, 3.39 to 10.51) puffs, p < 0.0005) times using e-cigarettes. No significant differences in the cumulative puff numbers were observed between the first and second e-cigarette visits at the 4-minute (1.98 (95% CI, -0.02 to 3.97) puffs, p = 0.053) and 5-minute (2.37 (95% CI, -0.05 to 4.79) puffs, p = 0.057) time points.

**Figure 3.2:** Cumulative number of puffs taken at various time points during the 5-minute smoking period, categorized by e-cigarette use order. Significant differences (*) in the cumulative number of puffs taken during the first two minutes of conditions were found between the first and second e-cigarette visits (p < 0.05). Values are expressed as mean ± standard error (SE).

### 3.2.2. Latin-Square Randomization to Account for Order Effects

To evaluate differences in smoking behavior between the experimental conditions, the cumulative number of puffs taken up until each minute time point (1-minute, 2-minute, 3-minute, 4-minute, 5-minute) were analyzed. A summary of the mean cumulative number of puffs taken can be found in Table 3.4 and Figure 3.3.
Table 3.4: Cumulative number of puffs taken at various time points during the 5-minute smoking period, categorized by experimental condition. Significant differences were found between the cumulative number of puffs taken at all time points during conditions ($p < 0.0005$). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between smoking conditions.

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Tobacco Cigarette</th>
<th>E-Cigarette with Placebo Lozenge</th>
<th>E-Cigarette with Nicotine Lozenge</th>
<th>F score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Minute</td>
<td>4.12 ± 1.44</td>
<td>5.46 ± 1.96</td>
<td>5.12 ± 1.14</td>
<td>10.432</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>2 Minute</td>
<td>7.02 ± 2.43</td>
<td>9.15 ± 3.41</td>
<td>8.93 ± 2.07</td>
<td>9.745</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>3 Minute</td>
<td>9.90 ± 3.51</td>
<td>12.93 ± 4.65</td>
<td>12.80 ± 3.69</td>
<td>10.654</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>4 Minute</td>
<td>12.44 ± 4.46</td>
<td>16.66 ± 5.96</td>
<td>16.68 ± 4.97</td>
<td>12.950</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>5 Minute</td>
<td>14.32 ± 5.35</td>
<td>20.20 ± 7.33</td>
<td>19.98 ± 5.81</td>
<td>15.518</td>
<td>&lt; 0.0005</td>
</tr>
</tbody>
</table>

A two-way repeated measures ANOVA was used to investigate the effect of various experimental conditions over time on the number of puffs taken. Mauchly’s Test of Sphericity found the assumption of sphericity was violated, $\chi^2(35) = 420.079$, $p = 0.027$. Using Greenhouse-Geisser calculations, an epsilon ($\varepsilon$) value of 0.290 was used to correct the two-way repeated measure ANOVA, and a statistically significant interaction was found between experimental conditions and time on the number of puffs taken, $F(2.322, 92.875) = 11.697$, $p < 0.0005$, partial $\eta^2 = 0.226$. Therefore, simple main effects were evaluated using repeated measures ANOVA.

During the first minute of the smoking period, significant differences in puff numbers were found between the conditions ($F(1.711, 68.447) = 10.432$, $p < 0.0005$, partial $\eta^2 = 0.207$) after corrections with a Huynh-Feldt calculation derived epsilon ($\varepsilon$) value of 0.856 to account for violations of sphericity. When smoking tobacco cigarettes, $4.12 \pm 1.44$ puffs were taken during the first minute while $5.46 \pm 1.96$ puffs and $5.12 \pm 1.14$ puffs were taken while using e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges respectively. Post hoc comparisons with a Bonferroni adjustment found the number of puffs taken while smoking tobacco cigarettes and e-cigarettes with placebo lozenges to be significantly different, with a mean difference of 1.34 (95% CI, 0.42 to 2.26) puffs, $p = 0.002$. A significant difference was also found between the number of puffs taken while smoking tobacco cigarettes and e-cigarettes with nicotine lozenges (1.00 (95% CI, 0.37 to 1.63) puffs, $p = 0.001$).

At the 2-minute time point, significant differences in cumulative puff numbers also were observed between conditions ($F(1.801, 72.051) = 9.745$, $p < 0.0005$, partial $\eta^2 = 0.196$) after corrections with epsilon ($\varepsilon$) 0.901. $7.02 \pm 2.43$ puffs had been taken from tobacco cigarettes, $9.15 \pm 3.41$ puffs were taken from e-cigarettes with placebo lozenges, and $8.93 \pm 2.07$ puffs were taken from e-cigarettes with nicotine lozenges. Post hoc comparisons revealed the number of puffs taken until the 2-minute time point was...
significantly different between smoking tobacco cigarettes and using e-cigarettes with placebo (2.12 (95% CI, 0.60 to 3.64) puffs, p = 0.004) and nicotine (1.90 (95% CI, 0.84 to 2.96) puffs, p < 0.0005).

The assumption of sphericity was not violated in the data regarding cumulative puffs taken until the 3-minute, 4-minute, and 5-minute time points, therefore no corrections were made. The mean number of puffs taken during the first 3 minutes was 9.90 ± 3.51 puffs when smoking tobacco cigarettes. 12.93 ± 4.65 puffs and 12.80 ± 3.69 puffs were taken when using e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges. Significant differences were found between conditions at the 3-minute time point, F(2, 80) = 10.654, p < 0.0005, partial $\eta^2 = 0.210$. Significant differences were observed between smoking tobacco cigarettes and e-cigarettes with placebo (3.02 (95% CI, 0.92 to 5.13) puffs, p = 0.003) and nicotine (2.90 (95% CI, 1.21 to 4.59) puffs, p < 0.0005) lozenges.

During the first four minutes of the smoking period, a mean of 12.44 ± 4.46 puffs were taken from tobacco cigarettes while 16.66 ± 5.96 puffs and 16.68 ± 4.97 puffs were taken from e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges respectively. Significant differences in cumulative puff number were observed, F(2,80) = 12.950, p < 0.0005, partial $\eta^2 = 0.245$. The cumulative number of puffs taken while smoking tobacco cigarettes was significantly lower than that from using e-cigarettes with placebo (4.22 (95% CI, 1.50 to 6.94) puffs, p = 0.001) and nicotine (4.24 (95% CI, 1.94 to 6.55) puffs, p < 0.0005).

Finally, significant differences in the total puff number at the 5-minute time point were observed between smoking conditions, F(2, 80) = 15.518, p < 0.0005, partial $\eta^2 = 0.280$. By the end of the smoking period, 14.32 ± 5.35 puffs had been smoked from tobacco cigarettes while 20.20 ± 7.33 puffs were taken from e-cigarettes with placebo lozenges. A mean of 19.89 ± 5.81 puffs were taken from e-cigarettes with nicotine lozenges. Post hoc analysis found significant differences in the total puff number between smoking tobacco cigarettes and using e-cigarettes with placebo (5.88 (95% CI, 2.40 to 9.35) puffs, p < 0.0005) and nicotine (5.66 (95% CI, 2.83 to 8.49), p < 0.0005) lozenges.

No significant differences in the cumulative number of puffs taken were observed between e-cigarettes with placebo and nicotine lozenges conditions at the 1-minute (-0.34 (95% CI, -1.05 to 0.37) puffs, p = 0.714), 2-minute (-0.22 (95% CI, -1.56 to 1.12) puffs, p = 1.000), 3-minute (-0.12 (95% CI, -1.87 to 1.62) puffs, p = 1.000), 4-minute (0.02 (95% CI, -2.12 to 2.17), p = 1.000), and 5-minute (-0.22 (95% CI -2.81 to 2.37) puffs, p = 1.000) time points.
Figure 3.3: Cumulative number of puffs taken at various time points during the 5-minute smoking period, categorized by experimental condition. In comparison to smoking tobacco cigarettes, significantly (*) more puffs were taken at all time points during both e-cigarette conditions (p < 0.05). No significant differences were found between e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges conditions at various time points (p > 0.05). Values are expressed as mean ± standard error (SE).

3.2.3. Number of Puffs Taken

During the tobacco cigarette condition, participants smoked 1.15 ± 0.36 cigarettes in the 5-minute period.

The total number of puffs taken while undergoing each experimental condition is presented in Table 3.5. Normality was violated and outliers were identified in the data regarding the number of puffs taken while undergoing the various experimental conditions. However, since the sources varied between conditions, all values were kept for data analysis. As such, a non-parametric Friedman test was used to investigate differences in the total number of puffs taken during each condition and a significant difference in the total puff number was found between the experimental conditions, \( \chi^2(2) = 23.404, p < 0.0005 \). A total of 14.32 ± 5.35 puffs were taken while smoking tobacco cigarettes, 20.20 ± 7.33 puffs were taken while using e-cigarettes with placebo lozenges, and 19.98 ± 5.81 puffs were taken while using e-cigarettes with nicotine lozenges. Post hoc pairwise comparisons were conducted with a Bonferroni correction for multiple comparisons. As previously mentioned in Section 3.2.2, the total number of puffs taken while smoking tobacco cigarettes was found to be significantly different from that of using e-cigarettes with placebo lozenges (p < 0.0005) and e-cigarettes with nicotine lozenges (p < 0.0005). No significant difference was observed between the total puff numbers from using e-cigarettes with placebo and nicotine lozenges (p = 1.000).
Table 3.5: Smoking topography by experimental condition. Significant differences in the number of puffs taken, total puff duration, mean puff duration, and mean IPI were found between smoking conditions (p < 0.0005). In comparison to tobacco cigarettes, more and longer puffs were taken with shorter IPI during e-cigarette conditions. Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the Friedman test and p-values shown reflect differences between smoking conditions.

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Number of Puffs (n)</th>
<th>Total Puff Duration (s)</th>
<th>Mean Puff Duration (s)</th>
<th>Total Interpuff Interval (s)</th>
<th>Mean Interpuff Interval (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarette</td>
<td>14.32 ± 5.35</td>
<td>24.29 ± 10.99</td>
<td>1.71 ± 0.55</td>
<td>234.46 ± 40.06</td>
<td>20.55 ± 8.87</td>
</tr>
<tr>
<td>E-Cigarette with Placebo Lozenge</td>
<td>20.20 ± 7.33</td>
<td>59.81 ± 31.30</td>
<td>2.94 ± 1.07</td>
<td>232.11 ± 48.85</td>
<td>13.62 ± 5.19</td>
</tr>
<tr>
<td>E-Cigarette with Nicotine Lozenge</td>
<td>19.98 ± 5.81</td>
<td>54.56 ± 22.54</td>
<td>2.78 ± 1.02</td>
<td>235.33 ± 24.17</td>
<td>13.66 ± 4.67</td>
</tr>
</tbody>
</table>

3.2.4. Puff Duration

The total and mean puff durations while undergoing each experimental condition are summarized in Table 3.5. A Friedman test was conducted to investigate differences in total puff duration between the experimental conditions since the data was not normally distributed and outliers were found. A significant difference was observed between the total puff durations of various smoking conditions, $\chi^2(2) = 45.122$, p < 0.0005. The total puff duration while smoking tobacco cigarettes was 24.29 ± 10.99 s, while that from using e-cigarettes with placebo and nicotine lozenges were 59.81 ± 31.30 s and 54.56 ± 22.54 s respectively. Post hoc pairwise comparisons with a Bonferroni correction found the total puff duration while smoking tobacco cigarettes to be significantly different from that of using e-cigarettes with placebo lozenges (p < 0.0005) and nicotine lozenges (p < 0.0005). No significant difference in the total puff duration was observed between using e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges (p = 1.000).

A one-way repeated measures ANOVA was conducted to evaluate differences in the mean puff duration while smoking tobacco cigarettes, e-cigarettes with placebo lozenges, and e-cigarettes with nicotine lozenges. While the data was normally distributed, outliers were observed. However, as the source of outliers varied between experimental conditions, all data points were kept for analysis. Mauchly’s Test of Sphericity found the assumption of sphericity was violated, $\chi^2(2) = 7.221$, p = 0.027. As a result, the one-way repeated measures ANOVA was corrected using epsilon (\(\varepsilon\)) 0.890, as calculated according to Huynh-Feldt. A significant difference in the mean puff duration was found between experimental conditions, $F(1.780, 71.189) = 41.249$, p < 0.0005, partial $\eta^2 = 0.508$. The mean puff duration while smoking tobacco cigarettes was 1.71 ± 0.55 s, while that of using e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges were 2.94 ± 1.07 s and 2.78 ± 1.02 s respectively. Post hoc analysis
with a Bonferroni adjustment found the mean puff duration from smoking tobacco cigarettes was significantly lower in comparison to using e-cigarette with placebo (1.23 (95% CI, 0.82 to 1.637) s, p < 0.0005) and nicotine lozenges (1.07 (95% CI, 0.67 to 1.47) s, p < 0.0005). No significant decrease in mean puff duration was found between using e-cigarettes with nicotine and placebo lozenges (0.16 (95% CI, -0.12 to 0.44) s, p = 0.482).

3.2.5. Interpuff Interval (IPI)

A summary of the total and mean interpuff intervals while undergoing each experimental condition can be found in Table 3. Friedman test were used to evaluate differences in the total and mean interpuff intervals (IPIs) from the various experimental conditions because outliers were identified and the data was not normally distributed.

The total IPI while smoking tobacco cigarettes was 234.46 ± 40.06 s, while that from using e-cigarettes with placebo lozenges and nicotine lozenges were 232.11 ± 48.85 s and 235.33 ± 24.17 s respectively. No significant differences in the total IPI were found between experimental conditions, $\chi^2(2) = 1.024$, p = 0.599.

The mean IPIs were significantly different between experimental conditions, $\chi^2(2) = 21.122$, p < 0.0005. The mean IPI while smoking tobacco cigarettes was 20.55 ± 8.87 s while that from using e-cigarettes with placebo lozenges and nicotine lozenges were 13.62 ± 5.19 s and 13.66 ± 4.67 s respectively. Pairwise comparisons were performed (SPSS) with a Bonferroni correction for multiple comparisons found significant differences between the mean IPIs from smoking tobacco cigarettes and e-cigarettes with placebo lozenges (p < 0.0005) and smoking tobacco cigarettes and e-cigarettes with nicotine lozenges (p < 0.0005). No significant difference observed between using e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges (p = 1.000).

3.3. Effectiveness of the Cue-Reactivity Paradigm

To evaluate the effectiveness of the cue-reactivity paradigm in inducing cigarette craving, the Brief Questionnaire of Smoking Urges (QSU-Brief) scores measured post-neutral cues presented were compared with those reported following the presentation of smoking cues one hour after smoking during the tobacco cigarette condition visit. Similarly, scores measure post-neutral cues administered three hours after smoking were compared to those measured post-smoking cues administered at that time. Significant increases were observed between scores reported post-neutral cues and post-smoking cues one hour (5.05 (95% CI, 2.28 to 7.81), p < 0.0005) and three hours (2.63 (95% CI, 1.20 to 4.07), p < 0.0005) after smoking tobacco cigarettes.

Moreover, in the QSU-Brief Factor 1 subscale data, significant increases were found between scores reported post-neutral cues and post-smoking cues one hour (2.93 (95% CI, 1.42 to 4.44), p < 0.0005)
and three hours (1.34 (95% CI, 0.50 to 2.18), p < 0.0005) after smoking tobacco cigarettes. In the QSU-Brief Factor 2 scores, significant increases were detected between scores reported post-neutral cues and post-smoking cues one hour (2.12 (95% CI, 0.47 to 3.77), p = 0.004) and three hours (1.29 (95% CI, 0.45 to 2.14), p < 0.0005) after smoking tobacco cigarettes. Similar increases in reported cigarette craving were observed in VAS measures (p < 0.0005).

These results suggest the cue-reactivity paradigm administered in the present study was effective in inducing cigarette craving in subjects both one hour and three hours after the initial condition administration.

3.4. Subjective Tobacco Craving Results

3.4.1. Visual Analogue Scale (VAS) – Cigarette Craving

As previously mentioned, five sets of questionnaires were administered during each study visit. The first set was completed at baseline, prior to administering the assigned experimental condition. One hour after the condition, participants were then presented neutral cues and then smoking cues. One set of questionnaires was completed following each cue presentation. Three hours after the initial condition, participants were again presented neutral cues and then smoking cues. Again, one set of questionnaires was completed following each cue presentation.

Outliers were found in the visual analogue scale (VAS) data regarding cigarette cravings. However, all data points were kept for analysis since the source of the outliers varied between experimental conditions and time points. Repeated measures ANOVA was used to investigate differences VAS cigarette craving scores.

In order to investigate changes in craving, VAS scores of items regarding cigarette craving were summated and summarized in Table 3.6. A mixed ANOVA was used to investigate various potential interaction effects in the Brief Questionnaire of Smoking Urges (QSU-Brief) data. An epsilon (ε) value of 0.504, as calculated according to Greenhouse-Geisser, was used to correct the analysis as Mauchly’s Test of Sphericity found the assumption of sphericity was violated, \( \chi^2(77) = 221.621, p < 0.0005 \). No significant Condition × Time × Group interaction (F(18.153, 223.892) = 1.436, p = 0.116, partial \( \eta^2 = 0.104 \)) was found. Similarly, no significant Condition × Group (F(8.394, 103.532) = 2.502, p = 0.074, partial \( \eta^2 = 0.169 \)), Time × Group (F(6.505, 80.229) = 1.166, p = 0.332, partial \( \eta^2 = 0.086 \)) interactions were found. A significant Condition × Time (F(6.051, 223.892) = 4.544, p < 0.0005, partial \( \eta^2 = 0.109 \)) interaction was found. Therefore, simple main effects were investigated.
Table 3.6: Cumulative VAS score when participants were asked to rate five phrases regarding cigarette craving. In comparison to baseline, significant reductions in cigarette craving were observed when assessed one hour after condition administration (p < 0.05). Smoking tobacco cigarettes produced the greatest craving reduction. Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th></th>
<th>Cumulative VAS Cigarette Craving Scores</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1-hr (Post Neutral Cues)</td>
</tr>
<tr>
<td>Tobacco Cigarettes</td>
<td>429.59± 96.15</td>
<td>270.78±140.70</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>430.41±72.42</td>
<td>356.07±112.06</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>428.24±95.02</td>
<td>329.54±146.50</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>412.66±103.48</td>
<td>314.32±145.08</td>
</tr>
</tbody>
</table>

No significant differences were found between the baseline VAS cigarette craving responses across all the experimental conditions (F(3, 120) = 0.872, p = 0.458).

During the tobacco cigarettes condition, significant differences in cumulative VAS craving responses were found (F(2.360, 94.403) = 38.998, p < 0.0005, partial η² = 0.494) after correcting with epsilon (ε) value 0.590 as calculated by Greenhouse-Geisser. Post hoc pairwise comparisons with a Bonferroni adjustment for multiple comparisons found significant reductions between baseline VAS scores and those reported post-neutral cues (-158.81 (95% CI, -221.03 to -96.58), p < 0.0005) and post-smoking cues (-84.85 (95% CI, -135.61 to -34.10), p < 0.0005) presented one hour after the initial 5-minute smoking condition. No significant differences were observed between baseline scores and those obtained post-neutral cues (-40.20 (95% CI, -84.02 to 3.63), p = 0.095) and post-smoking cues (-10.81 (95% CI, -46.49 to 24.89), p = 1.000) presented three hours after the initial condition.

Significant differences in scores were also observed during the e-cigarettes with placebo lozenges F(2.306, 92.235) = 10.943, p < 0.0005, partial η² = 0.215), e-cigarettes with nicotine lozenges (F(2.091, 83.635) = 12.810, p < 0.0005, partial η² = 0.243), and nicotine lozenges alone (F(2.101, 84.026) = 20.260, p < 0.0005, partial η² = 0.336) conditions after correcting with epsilon (ε) values 0.576, 0.523, and 0.525 respectively.
Pairwise comparisons found scores were significantly decreased between baseline and post-neutral cues presented one hour after using the e-cigarettes with placebo lozenges (-74.34 (95% CI, -121.66 to -27.03), p < 0.0005). Significant reductions in craving were reported between baseline and post-neutral cues (-98.71 (95% CI, -161.31 to -36.11), p < 0.0005) and post-smoking cues (-88.29 (95% CI, -154.10 to -22.49), p = 0.003) presented one hour after using e-cigarettes with nicotine lozenges. Similarly, during the nicotine lozenges alone condition, significant reductions were observed between baseline scores and those reported post-neutral cues (-98.34 (95% CI, -146.15 to -50.53), p < 0.0005) and post-smoking cues (-65.07 (95% CI, -113.45 to -16.70), p = 0.003) presented one hour after the condition.

To evaluate cue-induced cravings, VAS craving scores reported post-neutral cues and post-smoking cues presented one hour after the initial condition were compared. Withdrawal-induced cravings were assessed by comparing changes between scores measured post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition. Findings are summarized in Figure 3.4.

Craving was significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (73.95 (95% CI, 36.80 to 111.11), p < 0.0005). Similarly, a significant increase in craving was observed between measures post-neutral cues presented one hour after smoking and those reported post-neutral cues (118.61 (95% CI, 71.92 to 165.30), p < 0.0005) and post-smoking cues (148.00, (95% CI, 94.80 to 201. 20), p < 0.0005) three hours after smoking.

A significant increase was found between VAS scores measured post-neutral cues and post-smoking cues administered one hour after using e-cigarettes with placebo lozenges (31.59 (95% CI, 0.81 to 62.36), p = 0.041). A significant increase was also observed between craving measured post-neutral cues presented one hour after the condition and post-neutral cues (46.63 (95% CI, 7.93 to 85.34), p = 0.009) and post-smoking cues (59.46 (95% CI, 20.87 to 98.06), p < 0.0005) presented three hours after the condition.

During the e-cigarettes with nicotine lozenges condition, no significant difference was identified between assessments conducted post-neutral cues and post-smoking cues administered one hour after the condition (10.42 (95% CI, -11.95 to 32.78), p = 1.000). However, a significant increase was detected between craving reported post-neutral cues presented one hour after the condition and post-neutral cues (48.34 (95% CI, 4.80 to 91.88), p = 0.020) and post-smoking cues (67.73 (95% CI, 15.39 to 120.07), p = 0.004) presented three hours after the condition.
During the nicotine lozenges alone condition, a significant increase was identified between scores reported post-neutral cues and post-smoking cues administered one hour after the condition (33.27 (95% CI, 10.78 to 55.76), p = 0.001). A significant increase was also observed between scores measured post-neutral cues presented one hour after the condition and post-neutral cues (69.95 (95% CI, 28.67 to 111.23), p < 0.0005) and post-smoking cues (88.90 (95% CI, 43.27 to 134.53), p < 0.0005) presented three hours after the condition.

**Figure 3.4:** Cumulative VAS scores from the five items regarding cigarette craving. In comparison to baseline, significant reductions in cigarette craving were observed when assessed one hour after condition administration (p < 0.05). Smoking tobacco cigarettes produced the greatest craving reduction. Significant (*) increases in craving were observed after presentation of smoking cues of one hour after administering tobacco cigarettes, e-cigarettes with placebo lozenges, and nicotine lozenges alone conditions (p < 0.05). Significant (*) increases in craving were observed after three hours after administration of conditions (p < 0.05). Values are expressed as mean ± standard error (SE).

To investigate the ability of various experimental conditions in reducing cue-induced and withdrawal-induced cravings, VAS craving scores measured at various time points were subtracted with those reported post-neutral cues administered one hour after the conditions and will be referred to as normalized craving scores (summarized in **Table 3.7**).
Table 3.7: Normalized VAS craving scores. Significant differences in cue-induced, withdrawal-induced, and end-of-visit cravings were found between experimental conditions (p < 0.0005). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between conditions.

<table>
<thead>
<tr>
<th>Normalized Cumulative VAS Craving Scores</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>E-Cigarettes w Placebo Lozenges</td>
</tr>
<tr>
<td>1-hr (Post Smoking Cues)</td>
<td>73.95 ± 80.07</td>
</tr>
<tr>
<td>3-hr (Post Neutral Cues)</td>
<td>118.61 ± 100.62</td>
</tr>
<tr>
<td>3-hr (Post Smoking Cues)</td>
<td>148.00 ± 114.65</td>
</tr>
</tbody>
</table>

Cue-induced cravings, assessed by the normalized scores reported post-smoking cues presented one hour after conditions, were significantly different between various conditions (F(2.773, 110.906) = 9.839, p < 0.0005, partial η² = 0.197) after correcting with epsilon (ε) 0.924 as calculated by Huynh-Feldt. Post hoc analysis with a Bonferroni adjustment detected significantly lower cue-induced cravings during the e-cigarettes with placebo lozenges (-42.37 (95% CI, -76.70 to -8.03), p = 0.009), e-cigarettes with nicotine lozenges (-63.54 (95% CI, -101.26 to -25.82), p < 0.0005), and nicotine lozenges alone (-40.68 (95% CI, -72.19 to -9.18), p = 0.005) conditions in comparison to smoking tobacco cigarettes.

Similarly, withdrawal induced cravings, evaluated by the normalized scores reported post-neutral cues presented three hours after conditions, were significantly different between conditions (F(3, 120) = 8.872, p < 0.0005, partial η² = 0.182). In comparison with smoking tobacco cigarettes, withdrawal-induced cravings were significantly lower during the e-cigarettes with placebo lozenges (-71.98 (95% CI, -120.04 to -23.91), p = 0.001), e-cigarettes with nicotine lozenges (-70.27 (95% CI, -120.23 to -20.30), p = 0.002) and nicotine lozenges alone (-48.66 (95% CI, -91.12 to -6.20), p = 0.017) conditions.

Cravings at the end of each visit, representing compounded cue and withdrawal-induced cravings, were similarly significantly different between conditions (F(3, 120) = 10.881, p < 0.0005, partial η² = 0.214). In comparison to the tobacco cigarette condition, post hoc analysis revealed significantly lower cravings measured during the e-cigarettes with placebo lozenges (-88.54 (95% CI, -138.15 to -38.93), p < 0.0005), e-cigarettes with nicotine lozenges (-80.27 (95% CI, -131.39 to -29.15), p = 0.001), and nicotine lozenges alone (-59.10 (95% CI, -105.49 to -12.70), p = 0.006) conditions.

An example of a VAS craving item is “I craving cigarettes right now”. When participants were asked to score the phrase, “I crave cigarettes right now”, significant differences in scores were also observed during the tobacco cigarettes (F(2.481, 99.258) = 31.978, p < 0.0005, partial η² = 0.444), e-cigarettes
with placebo lozenges (F(2.828, 113.119) = 9.191, p < 0.0005, partial $\eta^2 = 0.187$), e-cigarettes with nicotine lozenges (F(2.314, 92.540) = 12.522, p < 0.0005, partial $\eta^2 = 0.238$), and nicotine lozenges alone (F(2.275, 91.018) = 15.069, p < 0.0005, partial $\eta^2 = 0.274$) conditions as summarized in Table 3.8.

**Table 3.8:** VAS Question 29 scores when participants were asked to rate the phrase, "I crave cigarettes right now". In comparison to baseline, significant reductions in craving were found when assessed one hour after condition administration (p < 0.05). Smoking tobacco cigarettes produced the greatest craving reduction. Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and $p$-values in the right-most column reflect differences between time points within each experimental condition. $P$-values shown in the bottom row reflect differences between conditions at each time point.

<table>
<thead>
<tr>
<th>VAS Cigarette Craving Questions Scores: Item 29</th>
<th>Baseline</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>$p$-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>87.17 ± 19.56</td>
<td>54.76 ± 31.28</td>
<td>67.83 ± 28.72</td>
<td>77.51 ± 25.36</td>
<td>85.20 ± 20.76</td>
<td>&lt; 0.0005 (31.978)</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>87.71 ± 16.42</td>
<td>71.07 ± 26.50</td>
<td>77.68 ± 24.03</td>
<td>80.68 ± 23.08</td>
<td>83.95 ± 22.58</td>
<td>&lt; 0.0005 (9.191)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>86.17 ± 20.76</td>
<td>64.80 ± 31.22</td>
<td>66.90 ± 32.42</td>
<td>75.20 ± 28.85</td>
<td>79.68 ± 28.15</td>
<td>&lt; 0.0005 (12.522)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>80.68 ± 25.59</td>
<td>59.78 ± 32.70</td>
<td>68.39 ± 31.05</td>
<td>76.76 ± 28.12</td>
<td>78.78 ± 27.43</td>
<td>&lt; 0.0005 (15.069)</td>
</tr>
</tbody>
</table>

Post hoc pairwise comparisons revealed significant decreases between baseline and scores reported post-neutral cues (-32.42 (95% CI, -45.74 to -19.09), p < 0.0005) and post-smoking cues (-19.34 (95% CI, -31.27 to -7.41), p < 0.0005) presented one hour after smoking tobacco cigarettes (see Figure 3.5). Similarly, during the e-cigarettes with placebo lozenges condition, significant decreases were found between baseline measures and scores reported post-neutral cues (-16.63 (95% CI, -28.34 to -4.93), p = 0.001) and post smoking-cues (-10.02 (95% CI, -19.84 to -0.21), p = 0.042) administered one hour after the condition. Significantly reduced cravings were detected baseline and post-neutral cues (-20.90 (95% CI, -32.72 to -9.09), p < 0.0005) and post-smoking cues (-12.29 (95% CI, -24.10 to -0.48), p = 0.036) administered one hour after using nicotine lozenges alone. During visits in which participants used e-cigarettes with nicotine lozenges, significant score reductions were observed between baseline and the post-neutral cues (-21.37 (95% CI, -33.68 to -9.06), p < 0.0005) and post-smoking cues (-19.27 (95% CI, -32.17 to -6.37), p = 0.001) presented one hour after the initial condition, as well as between baseline
and post-neutral cues (-10.98 (95% CI, -21.44 to -0.52), p = 0.034) presented three hours after the condition.

![VAS Item 29: "I crave cigarettes right now"](image)

**Figure 3.5**: VAS Question 29 scores when participants were asked to rate the phrase, “I crave cigarettes right now”. In comparison to baseline, significant reductions in craving were found when assessed one hour after condition administration (p < 0.05). Smoking tobacco cigarettes produced the greatest craving reduction. Values are expressed as mean ± standard deviation (SD). P-values in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at each time point.

3.4.2. **Brief Questionnaire of Smoking Urges (QSU-Brief)**

A mixed ANOVA was used to investigate various potential interaction effects in the Brief Questionnaire of Smoking Urges (QSU-Brief) data. An epsilon (ε) value of 0.474, as calculated according to Greenhouse-Geisser, was used to correct the analysis as Mauchly’s Test of Sphericity found the assumption of sphericity was violated, χ²(77) = 272.863, p < 0.0005. No significant Condition × Time × Group interaction (F(17.236, 212.572) = 1.555, p = 0.077, partial η² = 0.112) was found. Similarly, no significant Condition × Group (F(8.397, 103.565) = 1.888, p = 0.066, partial η² = 0.133), Time × Group (F(6.203, 76.509) = 0.766, p = 0.603, partial η² = 0.058), and Condition × Time (F(5.745, 212.572) = 1.405, p = 0.216, partial η² = 0.037) interactions were found. Therefore, simple main effects were investigated.
Outliers were found in the data regarding the total Brief Questionnaire of Smoking Urges (QSU-Brief) scores. Since the source of the outliers varied between experimental conditions and time points, all data points were kept for analysis. Repeated measures ANOVA analysis was conducted to evaluate differences in the total QSU-Brief scores between conditions and various time points (summarized in Table 3.9).

**Table 3.9**: Total QSU-Brief scores. In comparison to baseline, significant reductions were reported when craving was measured one hour after condition administration (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th>QSU-Brief Scores</th>
<th>Baseline</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>55.93 ± 11.32</td>
<td>44.68 ± 12.21</td>
<td>49.73 ± 13.40</td>
<td>52.98 ± 12.28</td>
<td>55.61 ± 11.70</td>
<td>&lt; 0.0005 (42.950)</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>57.05 ± 8.14</td>
<td>48.07 ± 12.09</td>
<td>51.95 ± 11.92</td>
<td>53.66 ± 11.91</td>
<td>56.22 ± 11.20</td>
<td>&lt; 0.0005 (19.796)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>57.93 ± 8.74</td>
<td>48.10 ± 14.55</td>
<td>49.90 ± 14.55</td>
<td>52.49 ± 13.06</td>
<td>55.49 ± 11.65</td>
<td>&lt; 0.0005 (19.208)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>56.24 ± 9.64</td>
<td>47.24 ± 14.43</td>
<td>49.59 ± 14.27</td>
<td>52.34 ± 12.85</td>
<td>55.07 ± 11.48</td>
<td>&lt; 0.0005 (19.164)</td>
</tr>
</tbody>
</table>

The mean baseline QSU-Brief scores were not significantly different between experimental conditions (F(3, 120) = 1.416, p = 0.241, partial $\eta^2 = 0.034$).

Significant differences in QSU-Brief scores at various time points were found during the tobacco cigarettes condition (F(2.850, 114.019) = 42.950, p < 0.0005, partial $\eta^2 = 0.518$) following corrections with epsilon ($\epsilon$) value 0.713 since Mauchly’s Test of Sphericity found the assumption of sphericity to be violated (p < 0.0005). Post hoc pairwise comparisons with a Bonferroni adjustment for multiple comparisons found significant decreases between baseline QSU-Brief scores and those measured post-neutral cues (-11.24 (95% CI, -15.10 to -7.39), p < 0.0005) and post-smoking cues (-6.20 (95% CI, -10.02 to -2.37), p < 0.005) presented one hour after the initial 5-minute smoking condition. No significant differences were observed between baseline scores and those obtained post-neutral cues (-2.95 (95%
CI, -6.26 to 0.36), p = 0.115) and post-smoking cues (-0.32 (95% CI, -3.50 to 2.87), p = 1.000) presented three hours after the initial condition.

Similarly, significant differences in QSU-Brief responses were observed during the e-cigarettes with placebo lozenges condition (F(2.346, 93.832) = 19.796, p < 0.0005, partial $\eta^2 = 0.331$) after corrections with epsilon (c) value 0.586. Post hoc pairwise comparisons with a Bonferroni adjustment found significant decreases in QSU-Brief scores between baseline and post-neutral cues (-8.98 (95% CI, -13.53 to -4.42), p < 0.0005) and post-smoking cues (-5.10 (95% CI, -9.10 to -1.09), p = 0.005) presented one hour after the initial condition. No significant differences were observed between baseline scores and those obtained post-neutral cues (-3.39 (95% CI, -7.55 to 0.77), p = 0.202) and post-smoking cues (-0.83 (95% CI, -4.30 to 2.64), p = 1.000) administered three hours after the initial condition.

During the e-cigarettes with nicotine lozenges condition, significant differences in QSU-Brief scores were observed (F(2.015, 80.591) = 19.208, p < 0.0005, partial $\eta^2 = 0.324$) with epsilon (c) corrections. Post hoc pairwise comparisons with a Bonferroni correction found significant decreases in QSU-Brief scores between baseline and post-neutral cues (-9.83 (95% CI, -15.15 to -4.51), p < 0.0005) and post-smoking cues (-8.02 (95% CI, -13.10 to -2.95), p < 0.0005) presented one hour after the initial condition. A significant reduction was also observed between baseline scores and those measured post-neutral cues (-5.44 (95% CI, -9.48 to -1.40), p = 0.003) presented three hours after the initial condition. No significant differences were observed between baseline scores and those obtained post-smoking cues (-2.44 (95% CI, -5.88 to 1.00), p = 0.415) administered three hours after the initial condition.

QSU-Brief scores were also significant differences during the nicotine lozenges alone condition (F(1.908, 76.334) = 19.164, p < 0.0005, partial $\eta^2 = 0.324$). Pairwise comparisons indicated significant reductions in baseline scores in comparison to those measured post-neutral cues (-9.00 (95% CI, -13.96 to -4.04), p < 0.0005) and post-smoking cues (-6.66 (95% CI, -11.25 to -2.07), p = 0.001) administered one hour after the initial condition. A significant decrease was also observed between baseline scores and those measured post-neutral cues (-3.90 (95% CI, -7.10 to -0.70), p = 0.008) administered three hours after the initial condition. No significant difference was observed between baseline scores and those obtained post-smoking cues (-1.17 (95% CI, -4.03 to 1.69), p = 1.000) presented three hours after the initial condition.

As previously mentioned, mean baseline QSU-Brief scores were not significantly different between experimental conditions (F(3, 120) = 1.416, p = 0.241, partial $\eta^2 = 0.034$). QSU-Brief scores reported post-neutral cues (F(3, 120) = 1.524, p = 0.212, partial $\eta^2 = 0.037$) and post-smoking cues (F(3, 120) = 0.664, p = 0.576, partial $\eta^2 = 0.016$) presented one hour later were not significantly different between conditions. Similarly, scores reported post-neutral cues (F(3, 120) = 0.287, p = 0.835, partial $\eta^2 = 0.007$)
and post-smoking cues \( (F(3, 120) = 0.255, p = 0.858, \text{partial } \eta^2 = 0.006) \) presented three hours after the initials conditions were not significantly different between conditions.

Cue-induced cravings were investigated by comparing changes between craving reported post-neutral cues and post-smoking cues presented one hour after the initial condition. Withdrawal-induced cravings were evaluated by comparing changes between measures reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition. Findings are summarized in Figure 3.6.

Craving was significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes \((5.05 (95\% \text{ CI, } 2.29 \text{ to } 7.81), p < 0.0005)\). Similarly, a significant increase in craving was observed between measures post-neutral cues presented one hour after smoking and those reported post-neutral cues \((8.29 (95\% \text{ CI, } 5.84 \text{ to } 10.75), p < 0.0005)\) and post-smoking cues \((10.93 (95\% \text{ CI, } 7.77 \text{ to } 14.08), p < 0.0005)\) three hours after smoking.

During the e-cigarettes with placebo lozenges condition, a significant increase was found between QSU-Brief scores measured post-neutral cues and post-smoking cues administered one hour after the condition \((3.88 (95\% \text{ CI, } 1.34 \text{ to } 6.42), p = 0.001)\). A significant increase was also observed between craving measured post-smoking cues presented one hour after the condition and post-neutral cues \((5.59 (95\% \text{ CI, } 2.22 \text{ to } 8.95), p < 0.0005)\) and post-smoking cues \((8.15 (95\% \text{ CI, } 3.93 \text{ to } 12.37), p < 0.0005)\) presented three hours after the condition.

A significant increase was observed between assessments post-neutral cues and post-smoking cues administered one hour after using e-cigarette with nicotine lozenges \((1.81 (95\% \text{ CI, } 0.15 \text{ to } 3.46), p = 0.024)\). A significant increase was detected between scores measured post-neutral cues presented one hour after the condition and post-neutral cues \((4.39 (95\% \text{ CI, } 0.28 \text{ to } 8.50), p = 0.029)\) and post-smoking cues \((7.39 (95\% \text{ CI, } 3.19 \text{ to } 11.59), p < 0.0005)\) presented three hours after the condition.

During the nicotine lozenges alone condition, a significant increase was detected between craving scores reported post-neutral cues and post-smoking cues administered one hour after the condition \((2.34 (95\% \text{ CI, } 0.33 \text{ to } 4.35), p = 0.013)\). A significant increase was found between measures post-neutral cues presented one hour after the condition and post-neutral cues \((5.10 (95\% \text{ CI, } 1.42 \text{ to } 8.77), p = 0.02)\) and post-smoking cues \((7.83 (95\% \text{ CI, } 3.47 \text{ to } 12.19), p < 0.0005)\) presented three hours after the condition.
Figure 3.6: Comparison of the Brief Questionnaire of Smoking Urges (QSU-Brief) scores between experimental conditions. In comparison to baseline, significant reductions in cigarette craving were observed when assessed one hour after condition administration (p < 0.05). Significant (*) increases in craving were observed after presentation of smoking cues of one hour after condition administration (p < 0.05). Significant (*) increases in craving were observed after three hours after condition administration (p < 0.05). Values are expressed as mean ± standard error (SE).

Similar to the VAS analysis previously conducted, QSU-Brief scores measured at various time points were subtracted with those reported post-neutral cues administered one hour after the conditions and will be referred to as normalized craving scores (summarized in Table 3.10).
Table 3.10: Normalized QSU-Brief craving scores. Significant differences in cue-induced and withdrawal-induced cravings were found between experimental conditions (p < 0.0005). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between conditions.

<table>
<thead>
<tr>
<th></th>
<th>Normalized Total QSU-Brief Scores</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tobacco Cigarettes</td>
<td>E-Cigarettes w Placebo Lozenges</td>
</tr>
<tr>
<td>1-hr (Post Smoking Cues)</td>
<td>5.05 ± 5.95</td>
<td>3.88 ± 5.48</td>
</tr>
<tr>
<td>3-hr (Post Neutral Cues)</td>
<td>8.29 ± 5.39</td>
<td>5.59 ± 7.26</td>
</tr>
<tr>
<td>3-hr (Post Smoking Cues)</td>
<td>10.93 ± 6.80</td>
<td>8.15 ± 9.09</td>
</tr>
</tbody>
</table>

Cue-induced cravings, evaluated by the normalized scores reported post-smoking cues presented one hour after conditions, were significantly different between various conditions (F(3, 120) = 6.092, p = 0.001, partial η² = 0.197). Post hoc analysis with a Bonferroni adjustment detected significantly lower cue-induced cravings during the e-cigarettes with nicotine lozenges (-3.24 (95% CI, -5.57 to -0.92), p = 0.002) and nicotine lozenges alone (-2.71 (95% CI, -5.25 to -0.17), p = 0.031) conditions in comparison to smoking tobacco cigarettes. However, no significant difference was observed between cue-induced cravings during the tobacco cigarette and e-cigarettes with placebo lozenges conditions (-1.17 (95% CI, -3.74 to 1.40), p = 1.000).

Similarly, withdrawal induced cravings, assessed by the normalized scores reported post-neutral cues presented three hours after conditions, were significantly different between conditions (F(3, 120) = 3.491, p = 0.018, partial η² = 0.080). No significant difference was detected between withdrawal-induced cravings during the tobacco cigarette and e-cigarettes with placebo lozenges conditions (-2.71 (95% CI, -5.96 to 0.54), p = 0.156). In comparison with smoking tobacco cigarettes, withdrawal-induced cravings were significantly lower during e-cigarettes with nicotine lozenges (-3.90 (95% CI, -7.77 to -0.04), p = 0.047) and nicotine lozenges alone (-3.20 (95% CI, -6.36 to -0.03), p = 0.046) conditions.

No significant differences in cravings at the end of each visit, representing compounded cue and withdrawal-induced cravings, were detected between conditions (F(3, 120) = 2.577, p = 0.057, η² = 0.061).
3.4.2.1. **Factor 1 Subscale**

A mixed ANOVA was conducted to investigate various interaction effects in the QSU-Brief Factor 1 subscale data. Mauchly’s Test of Sphericity found the assumption of sphericity was violated, $\chi^2(77) = 258.562, p < 0.0005$. An epsilon ($\varepsilon$) value of 0.455, as calculated according to Greenhouse-Geisser, was used to correct the analysis for multiple comparisons. No significant Condition × Time × Group interaction ($F(16.373, 201.940) = 1.367, p = 0.159$, partial $\eta^2 = 0.100$) was found. Similarly, no significant Condition × Group ($F(7.952, 98.073) = 1.969, p = 0.059$, partial $\eta^2 = 0.138$), Time × Group ($F(5.695, 70.236) = 0.676, p = 0.662$, partial $\eta^2 = 0.052$), and Condition × Time ($F(5.458, 16.373) = 1.666, p = 0.138$, partial $\eta^2 = 0.043$) interactions were found. Therefore, simple main effects were investigated.

The data regarding the Brief Questionnaire of Smoking Urges (QSU-Brief) Factor 1 subscale scores contained outliers. However, all the data points were kept for analysis since the source of the outliers varied between experimental conditions and time points. Repeated measures ANOVA analysis was conducted to evaluate differences in the QSU-Brief Factor 1 subscale scores between conditions and various time points (summarized in **Table 3.11**).

**Table 3.11**: QSU-Brief Factor 1 scores. In comparison to baseline, significant decreases were reported when craving was measured one hour after condition administration ($p < 0.05$). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th>QSU-Brief Factor 1 Subscale Scores</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>1-hr (Post Neutral Cues)</td>
</tr>
<tr>
<td>Tobacco Cigarettes</td>
<td>$31.32 \pm 4.37$</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>$31.98 \pm 2.54$</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>$31.95 \pm 2.85$</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>$31.02 \pm 3.75$</td>
</tr>
<tr>
<td>p-value (F score)</td>
<td>$0.175$</td>
</tr>
</tbody>
</table>
The baseline QSU-Brief scores were not significantly different between experimental conditions (F(2.456, 98.234) = 1.728, p = 0.175, partial \( \eta^2 = 0.041 \)) after correcting with epsilon (\( \varepsilon \)) 0.819, as calculated by Huynh-Feldt.

The QSU-Brief Factor 1 subscale scores at various time points were significant different during the tobacco cigarettes condition (F(2.779, 111.143) = 40.068, p < 0.0005, partial \( \eta^2 = 0.500 \)) after correcting with epsilon (\( \varepsilon \)) 0.695, as calculated by Greenhouse-Geisser. Post hoc pairwise comparisons with a Bonferroni adjustment for multiple comparisons found significant decreases between baseline scores and those reported post-neutral cues (-6.17 (95% CI, -8.35 to -3.99), p < 0.0005) and post-smoking cues (-3.24 (95% CI, -5.37 to -1.12), p = 0.001) presented one hour after the initial 5-minute smoking condition. No significant differences were observed between baseline scores and those measured post-neutral cues (-1.66 (95% CI, -3.51 to 0.19), p = 0.111) and post-smoking cues (-0.32 (95% CI, -2.09 to 1.46), p = 1.000) presented three hours after the initial condition (see Figure 3.7).

During the e-cigarettes with placebo lozenges condition, Factor 1 subscale scores were also significantly different (F(2.666, 106.621) = 17.318, p < 0.0005, partial \( \eta^2 = 0.302 \)) after correcting with epsilon (\( \varepsilon \)) 0.666. Pairwise comparisons identified significant reductions between baseline scores and those obtained post-neutral cues (-4.12 (95% CI, -6.26 to -1.98), p < 0.0005) and post-smoking cues (-2.29 (95% CI, -4.20 to -0.39), p = 0.009) presented one hour after the initial condition. No significant differences were found between baseline scores and those measured post-neutral cues (-1.66 (95% CI, -3.33 to 0.31), p = 0.180) and post-smoking cues (-0.34 (95% CI, -1.84 to 1.15), p = 1.000) presented three hours after the condition.

Similarly, significant differences in subscale scores were observed during the e-cigarettes with nicotine lozenges condition (F(1.822, 72.899) = 14.042, p < 0.0005, partial \( \eta^2 = 0.284 \)) following epsilon (\( \varepsilon \)) 0.453 corrections. Post hoc analysis revealed significant decreases between baseline and scores measured post-neutral cues (-5.29 (95% CI, -8.43 to -2.16), p < 0.0005) and post-smoking cues (-4.32 (95% CI, -7.41 to -1.22), p = 0.002) administered one hour after the initial condition. A significant decrease in QSU-Brief Factor 1 scores were also observed between baseline and those reported post-neutral cues presented three hours after the initial condition (-2.73 (95% CI, -5.04 to -0.43), p = 0.011). No significant difference in scores was observed between baseline and post-smoking cues administered three hours after the condition (-1.39 (95% CI, -3.13 to 0.35), p = 0.224).

Significant differences in Factor 1 scores were identified during the lozenge alone condition (F(1.810, 72.405) = 15.844, p < 0.0005, partial \( \eta^2 = 0.284 \)) following epsilon (\( \varepsilon \)) 0.453 corrections. Post hoc analysis revealed significant reductions between baseline scores and those reported post-neutral cues (-4.34 (95% CI, -7.34 to -1.35), p = 0.001) and post-smoking cues (-3.00 (95% CI, -5.73 to -0.28), p = 0.022) presented one hour after the initial condition. No significant differences were found between baseline scores and those reported post-
neutral cues (-1.44 (95% CI, -3.38 to 0.50), p = 0.332) and post-smoking cues (-0.15 (95% CI, -1.66 to 1.37), p = 1.000) administered three hours after the condition.

As mentioned, mean baseline QSU-Brief Factor 1 subscale scores were not significantly different between experimental conditions (F(2, 4.56, 98.234) = 1.728, p = 0.175, partial $\eta^2 = 0.041$) correcting with epsilon ($\omega$) 0.819. QSU-Brief scores reported post-neutral cues (F(3, 120) = 2.043, p = 0.111, partial $\eta^2 = 0.049$) and post-smoking cues (F(3, 120) = 1.297, p = 0.279, partial $\eta^2 = 0.031$) presented one hour later were not significantly different between conditions. Similarly, scores reported post-neutral cues (F(3, 120) = 0.686, p = 0.563, partial $\eta^2 = 0.017$) and post-smoking cues (F(3, 120) = 0.773, p = 0.511, partial $\eta^2 = 0.019$) presented three hours after the initial conditions were not significantly different between conditions.

Similar to the procedure conducted on the total QSU-Brief scores, cue-induced cravings were evaluated by comparing changes between craving reported post-neutral cues and post-smoking cues presented one hour after the initial condition while withdrawal-induced cravings were assessed by comparing changes between measures reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition. Findings are summarized in Figure 3.7.

Factor 1 subscale scores were significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (2.93 (95% CI, 1.42 to 4.44), p < 0.0005). Similarly, a significant increase was observed between scores reported post-neutral cues presented one hour after smoking and those reported post-neutral cues (4.51 (95% CI, 3.22 to 5.81), p < 0.0005) and post-smoking cues (5.85 (95% CI, 4.05 to 7.66), p < 0.0005) presented three hours after smoking.

A significant increase was identified between assessments post-neutral cues and post-smoking cues administered one hour after using e-cigarette with placebo lozenges (1.83 (95% CI, 0.45 to 3.21), p = 0.003). A significant increase was also found between scores measured post-neutral cues presented one hour after the condition and post-neutral cues (2.61 (95% CI, 0.85 to 4.37), p = 0.001) and post-smoking cues (3.78 (95% CI, 1.67 to 5.89), p < 0.0005) presented three hours after the condition.

During the e-cigarettes with nicotine lozenges condition, a significant increase was found between QSU-Brief scores measured post-neutral cues and post-smoking cues administered one hour after the condition (0.98 (95% CI, 0.12 to 1.83), p = 0.016). A significant increase was observed between craving measured post-neutral cues presented one hour after the condition and post-neutral cues (2.56 (95% CI, 0.11 to 5.01), p = 0.035) and post-smoking cues (3.90 (95% CI, 1.50 to 6.30), p < 0.0005) presented three hours after the condition.

During the nicotine lozenges alone condition, a significant increase was observed between craving scores reported post-neutral cues and post-smoking cues administered one hour after the condition (1.34 (95% CI, 0.16 to 2.53), p = 0.017). A significant increase was identified between craving measured...
post-neutral cues presented one hour after the condition and post-neutral cues (2.90 (95% CI, 0.76 to 5.05), \( p = 0.002 \)) and post-smoking cues (4.20 (95% CI, 1.66 to 6.73), \( p < 0.0005 \)) administered three hours after the condition.

![QSU-Brief: Factor 1](image)

**Figure 3.7:** Comparison of the Brief Questionnaire of Smoking Urges (QSU-Brief) Factor 1 subscale scores between experimental conditions. In comparison to baseline, significant reductions were found when cigarette craving was measured one hour after condition administration (\( p < 0.05 \)). Significant (*) increases in craving were observed after presentation of smoking cues of one hour after condition administration (\( p < 0.05 \)). Significant (*) increases in craving were observed after three hours after administration of conditions (\( p < 0.05 \)). Values are expressed as mean ± standard error (SE).

QSU-Brief Factor 1 subscale scores measured at various time points were then subtracted with those reported post-neutral cues administered one hour after the conditions (summarized in Table 3.12).
Table 3.12: Normalized QSU-Brief Factor 1 subscale craving scores. Significant differences in cue-induced and withdrawal-induced cravings were found between experimental conditions (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between conditions.

<table>
<thead>
<tr>
<th></th>
<th>Tobacco Cigarettes</th>
<th>E-Cigarettes w Placebo Lozenges</th>
<th>E-Cigarettes w Nicotine Lozenges</th>
<th>Lozenges Alone</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-hr (Post Smoking Cues)</td>
<td>2.93 ± 3.25</td>
<td>1.83 ± 2.97</td>
<td>0.98 ± 1.85</td>
<td>1.34 ± 2.56</td>
<td>0.001 (5.708)</td>
</tr>
<tr>
<td>3-hr (Post Neutral Cues)</td>
<td>4.51 ± 2.79</td>
<td>2.61 ± 3.79</td>
<td>2.56 ± 5.28</td>
<td>2.90 ± 4.62</td>
<td>0.046 (2.750)</td>
</tr>
<tr>
<td>3-hr (Post Smoking Cues)</td>
<td>5.85 ± 3.88</td>
<td>3.78 ± 4.55</td>
<td>3.90 ± 5.18</td>
<td>4.20 ± 5.46</td>
<td>0.056 (2.587)</td>
</tr>
</tbody>
</table>

Cue-induced cravings were significantly different between various conditions (F(3, 120) = 5.708, p = 0.001, partial $\eta^2 = 0.125$). In comparison to the tobacco cigarette condition, post hoc analysis with a Bonferroni adjustment detected significantly lower cue-induced cravings during the e-cigarettes with nicotine lozenges (-1.95 (95% CI, -3.30 to -0.61), p = 0.001) and nicotine lozenges alone (-1.59 (95% CI, -3.14 to -0.03), p = 0.043) conditions. However, no significant difference was observed between cue-induced cravings during the tobacco cigarette and e-cigarettes with placebo lozenges conditions (-1.10 (95% CI, -2.43 to 0.23), p = 0.163).

Similarly, withdrawal induced cravings were significantly different between conditions (F(3, 120) = 2.750, p = 0.046, partial $\eta^2 = 0.064$). In comparison with smoking tobacco cigarettes, withdrawal-induced cravings were significantly lower during e-cigarettes with placebo lozenges condition (-1.90 (95% CI, -3.68 to -0.13), p = 0.030). No significant difference was detected between withdrawal-induced cravings during the tobacco cigarette and e-cigarettes with nicotine lozenges (-1.95 (95% CI, -4.53 to 0.62), p = 0.251) as well as between the tobacco and nicotine lozenges alone (-1.61 (95% CI, -3.57 to 0.35), p = 0.167) conditions.

No significant differences in cravings at the end of each visit, representing compounded cue and withdrawal-induced cravings, were detected between conditions (F(3, 120) = 2.587, p = 0.056, $\eta^2 = 0.061$).
3.4.2.2. Factor 2 Subscale

A mixed ANOVA was conducted to investigate interaction effects in the QSU-Brief Factor 2 subscale data. Epsilon (\(\varepsilon\)) value 0.551 was used to correct for multiple comparisons since Mauchly’s Test of Sphericity found the assumption of sphericity was violated, \(\chi^2(77) = 184.026, p < 0.0005\). A significant Condition × Time × Group interaction \(F(19.842, 244.722) = 1.643, p = 0.044, \text{partial } \eta^2 = 0.118\) was detected. However, no significant Condition × Group \(F(8.558, 105.554) = 1.612, p = 0.125, \text{partial } \eta^2 = 0.116\), Time × Group \(F(7.109, 87.673) = 0.951, p = 0.473, \text{partial } \eta^2 = 0.052\), and Condition × Time \(F(6.614, 244.722) = 0.976, p = 0.447, \text{partial } \eta^2 = 0.026\) interactions were found. Therefore, simple main effects were investigated.

The data regarding the total Brief Questionnaire of Smoking Urges (QSU-Brief) Factor 2 scores contained outliers. However, the source of the outliers varied between experimental conditions and time points, therefore all the data points were kept for analysis. Repeated measures ANOVA analysis was conducted to evaluate differences in the QSU-Brief Factor 2 subscale scores between conditions and various time points (summarized in Table 3.13).

**Table 3.13**: QSU-Brief Factor 2 scores. In comparison to baseline, significant reductions were reported when craving was assessed one hour after condition administration (\(p < 0.05\)). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th>QSU-Brief Factor 2 Subscale Scores</th>
<th>Baseline</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>24.61 ± 8.01</td>
<td>19.54 ± 7.29</td>
<td>21.66 ± 8.39</td>
<td>23.32 ± 7.87</td>
<td>24.61 ± 7.68</td>
<td>&lt; 0.0005 (31.027)</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>25.07 ± 6.65</td>
<td>20.22 ± 7.57</td>
<td>22.27 ± 7.87</td>
<td>23.20 ± 8.47</td>
<td>24.59 ± 7.94</td>
<td>&lt; 0.0005 (16.319)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>25.83 ± 6.69</td>
<td>21.44 ± 7.87</td>
<td>22.27 ± 8.09</td>
<td>23.27 ± 7.80</td>
<td>24.93 ± 7.74</td>
<td>&lt; 0.0005 (14.708)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>25.22 ± 6.50</td>
<td>20.56 ± 8.03</td>
<td>21.56 ± 8.33</td>
<td>22.76 ± 8.06</td>
<td>24.20 ± 7.65</td>
<td>&lt; 0.0005 (19.377)</td>
</tr>
</tbody>
</table>
| p-value (F score)                 | 0.382      | 0.202                    | 0.792                    | 0.897                    | 0.783                    | (1.029) (1.562) (0.346) (0.198) (0.332)
No significant differences were found between the baseline QSU-Brief Factor 2 subscale scores from all the experimental conditions (F(3, 120) = 1.029, p = 0.382, partial $\eta^2 = 0.025$).

Significant differences were observed between QSU-Brief Factor 2 subscale scores at various time points during the tobacco cigarettes condition (F(3.068, 122.717) = 31.027, p < 0.0005, partial $\eta^2 = 0.437$) after correcting with epsilon ($\epsilon$) 0.767. Post hoc pairwise comparisons with a Bonferroni adjustment for multiple comparisons identified significant decrease between baseline Factor 2 scores and those reported post-neutral cues (-5.07 (95% CI, -7.18 to -2.96), p < 0.0005) and post-smoking cues (-2.95 (95% CI, -4.90 to -1.00), p = 0.001) presented one hour after the initial 5-minute smoking condition. No significant differences were observed between baseline scores and those measured post-neutral cues (-1.29 (95% CI, -3.04 to 0.45), p = 0.337) and post-smoking cues (0.00 (95% CI, -1.71 to 1.71), p = 1.000) presented three hours after the initial condition.

The Factor 2 scores were also significantly different during the e-cigarettes with placebo lozenges condition (F(2.412, 96.490) = 16.319, p < 0.0005, partial $\eta^2 = 0.290$) after corrections with epsilon ($\epsilon$) 0.603. Pairwise comparisons found significant reductions between baseline and scores reported post-neutral cues (-4.85 (95% CI, -7.48 to -2.23), p < 0.0005) and post-smoking cues (-2.81 (95% CI, -5.16 to -0.45), p = 0.010) presented one hour after the initial condition. No significant differences were observed between baseline scores and those measured post-neutral cues (-1.88 (95% CI, -4.53 to 0.78), p = 0.418) and post-smoking cues (-0.49 (95% CI, -2.71 to 1.74), p = 1.000) presented three hours after the condition.

Similarly, during the e-cigarettes with nicotine lozenges condition, significant differences in Factor 2 scores were observed (F(2.522, 100.868) = 14.708, p < 0.0005, partial $\eta^2 = 0.269$) after corrections with epsilon ($\epsilon$) 0.630. Post hoc analysis revealed significant decrease between baseline scores and those measured post-neutral cues (-4.39 (95% CI, -7.04 to -1.74), p < 0.0005) and post-smoking cues (-3.56 (95% CI, -5.88 to -1.24), p < 0.0005) administered one hour after the condition. A significant reduction was also found between baseline scores and those reported post-neutral cues presented three hours after the initial condition (-2.56 (95% CI, -4.64 to -0.49), p = 0.007). No significant differences were observed between scores measured at baseline and post-smoking cues presented three hours after the condition (-0.90 (95% CI, -2.95 to 1.15), p = 1.000).

The lozenges alone condition produced significantly different QSU-Brief Factor 2 subscale scores across the time points (F(2.347, 93.889) = 19.377, p < 0.0005, partial $\eta^2 = 0.326$) after correcting with epsilon ($\epsilon$) 0.587. Pairwise comparisons revealed scored reported at baseline to be significantly reduction from those measured post-neutral cues (-4.66 (95% CI, -6.99 to -2.33), p < 0.0005) and post-smoking cues (-3.66 (95% CI, -5.83 to -1.49), p < 0.0005) presented one hour after the initial condition. A significant decrease was also revealed between baseline measures and those reported post-neutral cues administered three hours after using lozenges (-2.46 (95% CI, -4.15 to -0.77), p = 0.001). No significant
difference was observed between baseline scores and those obtained post-smoking cues (-1.02 (95% CI, -2.70 to 0.65), p = 0.772) presented three hours after the initial condition.

Baseline QSU-Brief Factor 2 subscale scores were not significantly different between experimental conditions (F(3, 120) = 1.029, p = 0.382, partial η² = 0.025). QSU-Brief scores reported post-neutral cues (F(3, 120) = 1.562, p = 0.202, partial η² = 0.038) and post-smoking cues (F(3, 120) = 0.346, p = 0.792, partial η² = 0.009) presented one hour later were not significantly different between conditions. Similarly, scores reported post-neutral cues (F(3, 120) = 0.198, p = 0.897, partial η² = 0.005) and post-smoking cues (F(2.730, 109.183) = 0.332, p = 0.783, partial η² = 0.008), after correcting with epsilon (ε) 0.910, presented three hours after the initial conditions were not significantly different between conditions.

Cue-induced cravings and withdrawal-induced cravings were then investigated. Factor 2 subscale scores were significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (2.12 (95% CI, 0.47 to 3.77), p = 0.004). Similarly, a significant increase was observed between craving reported post-neutral cues presented one hour after smoking and those reported post-neutral cues (3.78 (95% CI, 2.22 to 5.34), p < 0.0005) and post-smoking cues (5.07 (95% CI, 3.36 to 6.79), p < 0.0005) three hours after smoking. Findings are summarized in Figure 3.8.

A significant increase were detected between craving measured post-neutral cues and post-smoking cues administered one hour after using e-cigarettes with placebo lozenges (2.05 (95% CI, 0.65 to 3.45), p = 0.001). A significant increase was also identified between craving reported post-neutral cues presented one hour after the condition and post-smoking cues (2.98 (95% CI, 0.95 to 5.00), p = 0.001) and post-smoking cues (4.37 (95% CI, 2.03 to 6.70), p < 0.0005) administered three hours after the condition.

During the e-cigarettes with nicotine lozenges condition, no significant increase was observed between QSU-Brief scores reported post-neutral cues and post-smoking cues administered one hour after the condition (0.83 (95% CI, -0.35 to 2.01), p = 0.429). Similarly, no significant change was identified between craving measured post-neutral cues presented one hour after the condition and post-neutral cues (1.83 (95% CI, -0.21 to 3.87), p = 0.111) and post-smoking cues (3.49 (95% CI, 1.11 to 5.87), p = 0.001) presented three hours after the condition.

Similarly, during the nicotine lozenges alone condition, no significant increase was detected between craving measured post-neutral cues and post-smoking cues administered one hour after the condition (1.00 (95% CI, -0.06 to 2.06), p = 0.077). However, a significant difference was observed between craving reported post-neutral cues presented one hour after the condition and post-neutral cues (2.20 (95% CI, 0.34 to 4.05), p = 0.011) and post-smoking cues (3.63 (95% CI, 1.49 to 5.82), p < 0.0005) presented three hours after the condition.
Figure 3.8: Comparison of the Brief Questionnaire of Smoking Urges (QSU-Brief) Factor 2 subscale scores between experimental conditions. In comparison to baseline, significant reductions were found when cigarette craving was measured one hour after condition administration ($p < 0.05$). Significant (*) increases in craving were observed after presentation of smoking cues of one hour after administration of tobacco cigarettes and e-cigarettes with placebo lozenges conditions ($p < 0.05$). Significant (*) increases in craving were observed after three hours after administration of tobacco cigarettes, e-cigarettes with placebo lozenges, and nicotine lozenges alone conditions ($p < 0.05$). Values are expressed as mean ± standard error (SE).

To investigate differences in cue-induced and withdrawal-induced cravings between conditions, QSU-Brief Factor 2 scores measured at various time points were subtracted with those reported post-neutral cues administered one hour after the conditions (summarized in Table 3.14).
Table 3.14: Normalized QSU-Brief Factor 2 subscale craving scores. Significant differences in cue-induced and withdrawal-induced cravings were found between experimental conditions (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between conditions.

<table>
<thead>
<tr>
<th></th>
<th>Tobacco Cigarettes</th>
<th>E-Cigarettes w Placebo Lozenges</th>
<th>E-Cigarettes w Nicotine Lozenges</th>
<th>Lozenges Alone</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-hr (Post Smoking Cues)</td>
<td>2.12 ± 3.55</td>
<td>2.05 ± 3.02</td>
<td>0.83 ± 2.54</td>
<td>1.00 ± 2.28</td>
<td><strong>0.012</strong> (3.787)</td>
</tr>
<tr>
<td>3-hr (Post Neutral Cues)</td>
<td>3.78 ± 3.36</td>
<td>2.98 ± 4.37</td>
<td>1.83 ± 4.40</td>
<td>2.20 ± 3.99</td>
<td><strong>0.032</strong> (3.033)</td>
</tr>
<tr>
<td>3-hr (Post Smoking Cues)</td>
<td>5.07 ± 3.69</td>
<td>4.37 ± 5.03</td>
<td>3.49 ± 5.12</td>
<td>3.63 ± 4.71</td>
<td><strong>0.148</strong> (1.817)</td>
</tr>
</tbody>
</table>

Cue-induced cravings were significantly different between various conditions (F(3, 120) = 3.787, p = 0.012, partial $\eta^2 = 0.086$). However, post hoc analysis with a Bonferroni adjustment detected no significant differences in cue-induced cravings between various conditions.

Withdrawal induced cravings were significantly different between conditions (F(3, 120) = 3.033, p = 0.032, partial $\eta^2 = 0.070$). In comparison with smoking tobacco cigarettes, withdrawal-induced cravings were significantly lower during e-cigarettes with nicotine lozenges condition (-1.95 (95% CI, -3.73 to -0.17), p = 0.025). No significant difference was detected between withdrawal-induced cravings during the tobacco cigarette and e-cigarettes with placebo lozenges (-0.81 (95% CI, -2.87 to 1.26), p = 1.000) as well as between the tobacco and nicotine lozenges alone (-1.59 (95% CI, -3.43 to 0.25), p = 0.129) conditions.

No significant differences in cravings at the end of each visit were detected between conditions (F(3, 120) = 1.817, p = 0.148, $\eta^2 = 0.043$).

3.5. Mood Assessments

3.5.1. Visual Analogue Scale (VAS) – Mood

At various time points throughout each study visit, participants completed a visual analogue scale (VAS) containing 24 questions regarding mood. Participants were asked to rate a variety of positive and negative effect related words, such as “Happy” and “Angry”, on a scale from 1 to 100 to indicate how much the word reflects their current mood.

In order to assess changes in mood at various time points, scores from positive and negative effect related words were summated and summarized in Table 3.15 and Table 3.16 respectively.
Table 3.15: VAS positive effect scores. In comparison to baseline, no significant differences in positive effect scores were found when mood was measured at various time points during each condition (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tobacco Cigarettes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td></td>
<td>497.61 ± 251.49</td>
<td>566.88 ± 245.29</td>
<td>480.32 ± 247.73</td>
<td>478.05 ± 240.65</td>
<td>451.27 ± 250.84</td>
<td>(8.276)</td>
</tr>
<tr>
<td><strong>E-Cigarettes w Placebo Lozenges</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>477.83 ± 244.18</td>
<td>462.17 ± 247.95</td>
<td>445.56 ± 246.54</td>
<td>421.93 ± 231.54</td>
<td>416.80 ± 236.55</td>
<td>(3.932)</td>
</tr>
<tr>
<td><strong>E-Cigarettes w Nicotine Lozenges</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>462.54 ± 280.05</td>
<td>469.88 ± 256.82</td>
<td>446.12 ± 242.85</td>
<td>447.98 ± 265.26</td>
<td>416.05 ± 258.75</td>
<td>(2.442)</td>
</tr>
<tr>
<td><strong>Lozenges Alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.141</td>
</tr>
<tr>
<td></td>
<td>483.93 ± 259.83</td>
<td>465.37 ± 255.68</td>
<td>438.12 ± 267.55</td>
<td>452.95 ± 255.41</td>
<td>439.24 ± 264.58</td>
<td>(1.917)</td>
</tr>
<tr>
<td><strong>p-value (F score)</strong></td>
<td>0.596</td>
<td>&lt; 0.0005</td>
<td>0.232</td>
<td>0.102</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.600)</td>
<td>(7.659)</td>
<td>(1.451)</td>
<td>(2.111)</td>
<td>(1.274)</td>
<td></td>
</tr>
</tbody>
</table>

No significant differences were found between the baseline VAS positive effect scores from all the experimental conditions (F(2.649, 105.945) = 0.600, p = 0.596) after correcting with epsilon (ε) 0.883 as calculated by Huynh-Feldt.

During the tobacco cigarette condition, significant differences were found between VAS scores at various time points (F(2.801, 112.051) = 8.276, p < 0.0005) after correcting with epsilon (ε) 0.700. Post hoc analysis found no significant differences between baseline scores and those reported at various time points (p > 0.05).

Similarly, during the e-cigarette with placebo lozenge visit, significant differences were detected in VAS scores (F(2.852, 114.063) = 3.932, p = 0.012) after epsilon (ε) 0.713 correction for multiple comparisons. However, post hoc analysis found no significant differences between baseline scores and those reported at various time points (p > 0.05).

No significant differences were also observed during the e-cigarettes with nicotine lozenges (F(2.782, 111.283) = 2.442, p = 0.073, partial η² = 0.058) and nicotine lozenges alone (F(2.521, 100.839) = 1.917, p = 0.141) conditions after correcting with epsilon (ε) 0.696 and 0.630 respectively.
Effects of cue-induced cravings and withdrawal-induced cravings were then investigated. VAS positive effect scores were significantly reduced between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (-86.56 (95% CI, -144.14 to -28.99), p = 0.001). Similarly, a significant reduction was observed between measures reported post-neutral cues presented one hour after smoking and those reported post-neutral cues three hours after smoking (-88.83 (95% CI, -144.90 to -32.76), p < 0.0005).

No significant changes were detected between positive effect scores measured post-neutral cues and post-smoking cues administered one hour after condition administration during the e-cigarettes with placebo lozenges (-16.61 (95% CI, -67.50 to 34.28), p = 1.000), e-cigarettes with nicotine lozenges (-23.76 (95% CI, -75.74 to 28.28), p = 1.000), and lozenges alone (-27.24 (95% CI, -20.90 to 75.39), p = 1.000) conditions. Similarly, no significant change was identified between scores post-neutral cues presented one hour after conditions and post-neutral cues presented three hours after conditions during the e-cigarettes with placebo lozenges (-40.24 (95% CI, -85.98 to 5.49), p = 0.149), e-cigarettes with nicotine lozenges (-21.90 (95% CI, -67.93 to 24.12), p = 1.0000), and nicotine lozenges (-12.42 (95% CI, -66.38 to 41.55), p = 1.000) visits.

Table 3.16: VAS negative effect scores. In comparison to baseline, significant decreases in negative effect scores were observed when mood was assessed one hour after administering tobacco cigarettes and e-cigarettes with placebo lozenges (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>420.29</td>
<td>310.44</td>
<td>361.00</td>
<td>375.93</td>
<td>414.85</td>
<td>0.001 (5.842)</td>
</tr>
<tr>
<td></td>
<td>± 310.99</td>
<td>± 280.12</td>
<td>± 258.61</td>
<td>± 274.72</td>
<td>± 300.63</td>
<td></td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>411.12</td>
<td>342.59</td>
<td>382.95</td>
<td>390.15</td>
<td>417.60</td>
<td>0.026 (3.272)</td>
</tr>
<tr>
<td></td>
<td>± 316.81</td>
<td>± 251.66</td>
<td>± 248.89</td>
<td>± 267.22</td>
<td>± 274.18</td>
<td></td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>420.71</td>
<td>404.90</td>
<td>430.71</td>
<td>427.29</td>
<td>466.78</td>
<td>0.160 (1.756)</td>
</tr>
<tr>
<td></td>
<td>± 301.31</td>
<td>± 293.50</td>
<td>± 275.50</td>
<td>± 287.21</td>
<td>± 295.78</td>
<td></td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>331.20</td>
<td>338.59</td>
<td>377.63</td>
<td>357.12</td>
<td>389.15</td>
<td>0.045 (2.902)</td>
</tr>
<tr>
<td></td>
<td>± 257.36</td>
<td>± 254.25</td>
<td>± 250.75</td>
<td>± 281.34</td>
<td>± 260.52</td>
<td></td>
</tr>
<tr>
<td>p-value (F score)</td>
<td>0.051</td>
<td>0.066</td>
<td>0.156</td>
<td>0.117</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3.003)</td>
<td>(2.666)</td>
<td>(1.884)</td>
<td>(2.063)</td>
<td>(1.790)</td>
<td></td>
</tr>
</tbody>
</table>
No significant differences were found between the baseline VAS negative effect scores from all the experimental conditions ($F(2.174, 86.953) = 3.003, p = 0.051$) after correcting with epsilon ($\epsilon$) 0.725 to account for multiple comparisons.

During the tobacco cigarette condition, significant differences were found between VAS scores at various time points ($F(2.931, 117.226) = 5.842, p = 0.001$) after correcting with epsilon ($\epsilon$) 0.733. Post hoc analysis with a Bonferroni adjustment found a significant decrease between baseline VAS negative effect scores and those reported post-neutral cues presented one hour after smoking (-109.85 (95% CI, -214.43 to -5.28), $p = 0.033$).

Similarly, during the e-cigarettes with placebo lozenges visit, significant differences were detected in scores ($F(2.808, 112.302) = 3.272, p = 0.026$) after epsilon ($\epsilon$) 0.702 correction. Post hoc comparisons revealed a significant decrease between baseline VAS scores and those reported post-neutral cues presented one hour after the condition (-68.54 (95% CI, -131.93 to -5.14), $p = 0.026$).

Significant differences in VAS scores were observed during the nicotine lozenges alone condition ($F(2.609, 104.374) = 2.902, p = 0.045$). However, post hoc analysis with a Bonferroni adjustment found no significant differences between scores reported at various time points. No significant differences were also observed during the e-cigarettes with nicotine lozenges condition ($F(2.969, 118.778) = 1.756, p = 0.160$, partial $\eta^2 = 0.042$) after correcting with epsilon ($\epsilon$) 0.742.

VAS negative effect scores were not significantly different between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (50.56 (95% CI, -30.01 to 131.13), $p = 0.294$). However, a significant increase was observed between measures reported post-neutral cues presented one hour after smoking and those reported post-neutral cues (65.49 (95% CI, 1.58 to 129.40), $p = 0.041$) and post-smoking cues (104.42 (95% CI, 15.00 to 193.83), $p = 0.013$) three hours after smoking.

No significant changes were detected between negative effect scores measured post-neutral cues and post-smoking cues administered one hour after conditions during the e-cigarettes with placebo lozenges (40.37 (95% CI, -16.82 to 97.55), $p = 0.423$), e-cigarettes with nicotine lozenges (25.81 (95% CI, -30.08 to 81.69), $p = 1.000$), and lozenges alone (39.05 (95% CI, -12.53 to 90.63), $p = 0.301$) visits. Similarly, no significant differences were observed between scores post-neutral cues presented one hour after conditions and post-neutral cues presented three hours after conditions during the e-cigarettes with placebo lozenges (47.56 (95% CI, -20.64 to 115.76), $p = 0.447$), e-cigarettes with nicotine lozenges (22.39 (95% CI, -45.05 to 89.83), $p = 1.000$), and nicotine lozenges (18.54 (95% CI, -31.92 to 68.99), $p = 1.000$) visits.
3.5.2. Positive and Negative Affect Scale (PANAS)

A mixed ANOVA was conducted to investigate interaction effects in the Positive and Negative Affect Scale (PANAS) positive affect data. Epsilon (\(\varepsilon\)) value 0.590, as calculated by Greenhouse-Geisser, was used to correct for multiple comparisons as Mauchly’s Test of Sphericity found the assumption of sphericity was violated, \(\chi^2(77) = 147.751, p < 0.0005\). Significant Condition × Time × Group (\(F(21.257, 262.164) = 1.926, p = 0.010, \text{partial } \eta^2 = 0.135\)) and Condition × Group (\(F(8.057, 99.370) = 2.793, p = 0.008, \text{partial } \eta^2 = 0.185\)) interactions were detected. However, pairwise comparisons found no significant differences between groups (\(p = 1.000\)). No significant Time × Group (\(F(7.228, 89.147) = 1.193, p = 0.314, \text{partial } \eta^2 = 0.088\)) and Condition × Time (\(F(7.086, 262.164) = 1.564, p = 0.145, \text{partial } \eta^2 = 0.041\)) interactions were found. Therefore, simple main effects were investigated.

Similarly, interaction effects of negative affect data was conducted with epsilon (\(\varepsilon\)) value 0.528 to correct for violations of sphericity, \(\chi^2(77) = 194.032, p < 0.0005\). No significant Condition × Time × Group interactions (\(F(18.990, 234.212) = 1.346, p = 0.156, \text{partial } \eta^2 = 0.098\)) was detected. No significant Condition × Group (\(F(7.357, 90.735) = 0.950, p = 0.475, \text{partial } \eta^2 = 0.072\)), Time × Group (\(F(9.266, 114.276) = 1.187, p = 0.309, \text{partial } \eta^2 = 0.088\)), and Condition × Time (\(F(6.330, 234.212) = 16.269, p = 0.198, \text{partial } \eta^2 = 0.037\)) interactions were found. Therefore, simple main effects were investigated.

A one-way repeated measures ANOVA was conducted to evaluate differences positive and negative affect scores from various experimental conditions. While the data was normally distributed for positive affect scores, it was the negative affect data was not normally distributed. Outliers were observed; however all data points were kept for analysis since the source of outliers varied between experimental conditions and time points. The one-way repeated measures ANOVA was corrected using epsilon values as calculated by Greenhouse Geisser. The positive and negative affect scores are summarized in Table 3.17 and Table 3.18 respectively.

No significant differences were found between the baseline PANAS positive affect (\(F(2.439, 97.559) = 0.475, p = 0.661\)) and negative affect (\(F(2.618, 104.702) = 1.355, p = 0.262\)) scores from all the experimental conditions.
Table 3.17: PANAS Positive Affect scores. In comparison to baseline, no significant differences in positive affect scores were observed when mood was assessed one hour after administering tobacco cigarettes and e-cigarettes with placebo lozenges (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th></th>
<th>PANAS Positive Affect (PA)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 1-hr (Post Neutral Cues) 1-hr (Post Smoking Cues) 3-hr</td>
<td></td>
</tr>
<tr>
<td>Tobacco Cigarettes</td>
<td>24.80 ± 8.07 24.44 ± 7.81 23.22 ± 7.67 23.37 ± 7.19 22.66 ± 7.50</td>
<td>0.036 (2.971)</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>25.85 ± 9.17 23.85 ± 8.89 23.39 ± 8.96 22.49 ± 7.80 21.88 ± 7.46</td>
<td>0.003 (5.759)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>24.66 ± 8.78 22.98 ± 9.16 22.76 ± 8.77 22.78 ± 9.14 23.02 ± 9.50</td>
<td>0.130 (2.013)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>24.63 ± 8.76 23.98 ± 8.05 23.17 ± 8.32 23.71 ± 8.14 23.44 ± 8.32</td>
<td>0.300 (1.235)</td>
</tr>
<tr>
<td>p-value (F score)</td>
<td>0.661 (0.475) 0.553 (0.667) 0.937 (0.139) 0.415 (0.944) 0.369 (1.050)</td>
<td></td>
</tr>
</tbody>
</table>

Post-hoc analysis a Bonferroni adjustment found no significant differences in positive affect scores reported during the tobacco cigarettes condition between baseline and scores measured post-neutral cues (-0.37 (95% CI, -2.86 to 2.13), p = 1.000) and post-smoking cues (-1.59 (95% CI, -4.43 to 1.26), p = 1.000) presented one hour after the initial smoking condition. No significant differences were also observed between baseline scores and those reported post-neutral cues (-1.44 (95% CI, -3.64 to 0.76), p = 0.591) and post-smoking cues (-2.15 (95% CI, -4.69 to 0.40), p = 0.165) administered three hours after smoking. Similar results were observed during the e-cigarettes with nicotine lozenges and lozenges alone conditions.

During the e-cigarettes with placebo lozenges condition, significant decreases were observed between positive affect scores measured at baseline and those reported post-neutral cues (-3.37 (95% CI, -6.66 to -0.07), p = 0.042) and post-smoking cues (-3.98 (95% CI, -7.85 to -0.10), p = 0.041) administered three hours after the initial condition.

No significant differences were detected between positive affect scores measured post-neutral cues and post-smoking cues administered one hour after conditions during all conditions (p > 0.05). Similarly, no significant differences were identified between measures post-neutral cues presented one hour after conditions and post-neutral cues presented three hours after conditions during all conditions (p > 0.05).
During the tobacco cigarettes condition, significant reductions were also observed between the negative affect scores measured at baseline and those reported post-neutral cues presented one hour after smoking (-2.88 (95% CI, -5.22 to -0.54), p = 0.007). Conversely, during the lozenges alone condition, significant increases were observed between baseline scores and those measured post-smoking cues administered three hours after the initial condition (1.61 (95% CI, 0.10 to 3.12), p = 0.029). No significant differences in negative affect scores were observed during e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges conditions (p > 0.05).

PANAS negative affect scores were significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (1.88 (95% CI, 0.36 to 3.40), p = 0.007). Similarly, a significant increase was observed between scores reported post-neutral cues presented one hour after smoking and those reported post-neutral cues (1.54 (95% CI, 0.10 to 2.98), p = 0.029) and post-smoking cues (3.00 (95% CI, 1.03 to 4.97), p = 0.001) three hours after smoking.

During the e-cigarettes with nicotine lozenges condition, a significant increase in negative affect scores were reported between post-neutral cues and post-smoking cues administered one hour after the condition (1.15 (95% CI, 0.07 to 2.22), p = 0.030). No significant difference was observed between scores reported post-neutral cues one hour after the condition and post-neutral cues three hours after the condition (1.02 (95% CI, -0.55 to 2.60), p = 0.559).

---

**Table 3.18**: PANAS Negative Affect scores. In comparison to baseline, a significant reduction in negative affect scores was reported when mood was measured one hour after administering tobacco cigarettes (p = 0.007). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown in the right-most column reflect differences between time points within each experimental condition. P-values shown in the bottom row reflect differences between conditions at various time points.

<table>
<thead>
<tr>
<th>Tobacco Cigarettes</th>
<th>Baseline</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>16.27 ± 7.21</td>
<td>15.05 ± 5.84</td>
<td>16.39 ± 6.94</td>
<td>15.76 ± 6.22</td>
<td>16.68 ± 6.42</td>
<td>0.042 (2.755)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>16.39 ± 6.63</td>
<td>15.15 ± 4.94</td>
<td>16.29 ± 5.81</td>
<td>16.17 ± 5.95</td>
<td>17.02 ± 5.62</td>
<td>0.102 (2.307)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>14.68 ± 4.70</td>
<td>14.71 ± 5.11</td>
<td>15.78 ± 6.23</td>
<td>14.98 ± 5.10</td>
<td>16.29 ± 5.97</td>
<td>0.008 (4.355)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p-value</th>
<th>0.262</th>
<th>0.143</th>
<th>0.626</th>
<th>0.350</th>
<th>0.824</th>
<th>(F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.143</td>
<td>(1.934)</td>
<td>(0.522)</td>
<td>(1.089)</td>
<td>(0.258)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
No significant changes were detected between negative affect scores measured post-neutral cues and post-smoking cues administered one hour after conditions during the e-cigarettes with placebo lozenges (1.34 (95% CI, -0.65 to 3.33), p = 0.522) and lozenges alone (1.07 (95% CI, -0.20 to 2.35), p = 0.146) visits. Similarly, no significant differences were observed between scores post-neutral cues presented one hour after conditions and post-neutral cues presented three hours after conditions during the e-cigarettes with placebo lozenges (0.71 (95% CI, -0.82 to 2.24), p = 1.000) and nicotine lozenges (0.27 (95% CI, -1.12 to 1.66), p = 1.000) visits.

3.6. Gender Differences

3.6.1. Demographics

Of the 41 participants who completed the study, 22 were female and 19 were male. In order to investigate potential gender effects on craving reduction, participants were categorized into two groups based on their genders. No significant differences in demographics were found between male and female participants. A summary of participant characteristics can be seen in Table 3.19.

Table 3.19: Baseline participant demographics categorized by gender. No significant differences were observed between genders. Values are expressed as mean ± standard deviation (SD). P-values shown reflect comparisons between genders.

<table>
<thead>
<tr>
<th>Sample (n=41)</th>
<th>Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>35.20 ± 10.97</td>
<td>32.18 ± 10.68</td>
</tr>
<tr>
<td>Employment Status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Time</td>
<td>8 (19.51)</td>
<td>3 (13.63)</td>
</tr>
<tr>
<td>Part Time</td>
<td>9 (21.95)</td>
<td>4 (18.18)</td>
</tr>
<tr>
<td>Self-Employed</td>
<td>6 (14.63)</td>
<td>3 (13.63)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>17 (41.47)</td>
<td>12 (54.55)</td>
</tr>
<tr>
<td>Retired</td>
<td>1 (2.44)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Currently a student (%)</td>
<td>6 (14.63)</td>
<td>5 (22.73)</td>
</tr>
<tr>
<td>Education of High School or less (%)</td>
<td>25 (60.98)</td>
<td>14 (63.64)</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>29 (70.73)</td>
<td>16 (72.73)</td>
</tr>
<tr>
<td>Age smoked first whole cigarette</td>
<td>15.05 ± 3.05</td>
<td>15.18 ± 2.06</td>
</tr>
<tr>
<td>Age smoked cigarettes occasionally</td>
<td>15.85 ± 3.14</td>
<td>15.73 ± 2.38</td>
</tr>
<tr>
<td>Age started smoking daily</td>
<td>17.61 ± 3.46</td>
<td>17.82 ± 2.52</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>19.68 ± 8.15</td>
<td>19.64 ± 8.64</td>
</tr>
<tr>
<td>FTND score</td>
<td>6.39 ± 2.00</td>
<td>6.32 ± 2.10</td>
</tr>
<tr>
<td>WHODAS score (%)</td>
<td>10.64 ± 2.85</td>
<td>11.66 ± 4.12</td>
</tr>
</tbody>
</table>
3.6.2. **Smoking Topography**

Women smoked $1.14 \pm 0.35$ tobacco cigarettes while men smoked $1.16 \pm 0.38$ tobacco cigarettes during the 5-minute condition.

The total number of puffs taken, total and mean puff duration, and total and mean interpuff interval (IPI) while undergoing each experimental condition are presented in Table 3.20. Normality was not violated. Outliers were identified in the data. However, since the sources varied between conditions, all values were kept for data analysis. As such, parametric repeated measures ANOVA, mixed ANOVA and univariate analysis of variance tests were used to evaluate differences in the smoking topography within and between genders.

Within each gender group, repeated measures ANOVA identified significant differences in the total number of puffs taken, the total and mean puff duration, and the mean IPI measured under various smoking conditions (summarized in the right-most column in Table 3.20, $p < 0.05$).

**Table 3.20**: Smoking topography during experimental conditions categorized by gender. Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between smoking conditions within each gender group.

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Tobacco Cigarette</th>
<th>E-Cigarette with Placebo Lozenge</th>
<th>E-Cigarette with Nicotine Lozenge</th>
<th>F score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Puffs (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15.36 ± 3.85</td>
<td>18.82 ± 5.54</td>
<td>20.36 ± 6.48</td>
<td>7.224</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>13.11 ± 6.58</td>
<td>21.79 ± 8.86</td>
<td>19.53 ± 5.07</td>
<td>10.211</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Total Puff Duration (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25.65 ± 8.82</td>
<td>53.91 ± 28.74</td>
<td>56.37 ± 22.67</td>
<td>25.753</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Male</td>
<td>22.71 ± 13.14</td>
<td>66.63 ± 33.49</td>
<td>52.47 ± 22.81</td>
<td>22.844</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Mean Puff Duration (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.70 ± 0.57</td>
<td>2.80 ± 1.04</td>
<td>2.86 ± 1.06</td>
<td>17.714</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Male</td>
<td>1.73 ± 0.54</td>
<td>3.11 ± 1.11</td>
<td>2.70 ± 1.00</td>
<td>28.123</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Total Interpuff Interval (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>239.38 ± 38.15</td>
<td>232.84 ± 46.90</td>
<td>233.11 ± 26.25</td>
<td>0.248</td>
<td>0.782</td>
</tr>
<tr>
<td>Male</td>
<td>228.77 ± 42.47</td>
<td>231.28 ± 52.31</td>
<td>237.90 ± 12.95</td>
<td>0.291</td>
<td>0.694</td>
</tr>
<tr>
<td>Mean Interpuff Interval (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17.73 ± 5.31</td>
<td>14.16 ± 5.20</td>
<td>13.35 ± 4.62</td>
<td>7.786</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>23.82 ± 11.00</td>
<td>12.98 ± 5.25</td>
<td>14.01 ± 4.83</td>
<td>18.028</td>
<td>&lt; 0.0005</td>
</tr>
</tbody>
</table>

When separated by gender, outliers were identified in the data regarding the total number of puffs taken, the mean and total puff duration, and the mean and total interpuff interval (IPI). However, since the source of the outliers varied between experimental conditions, all data points were kept for analysis.
Moreover, the data was normally distributed. As a result, the parametric mixed ANOVA was used to investigate differences in smoking topography between male and female participants.

Levene’s test of homogeneity of variance was used to determine there was homogeneity of variances (p > 0.05). No statistically significant interaction was observed between gender and the total number of puffs taken during each experimental condition (F(1.923, 74.979) = 2.646, p = 0.080) after corrections with epsilon (ε) 0.961 as calculated by Huynh-Feldt. The main effect of gender showed no significant differences in the total number of puffs taken between genders, F(1, 39) = 0.001, p = 0.976, partial η² = 0.000. Similarly, no significant interactions were observed between gender and the mean puff duration of various smoking conditions (F(1.762, 68.725) = 1.328, p = 0.270) after correcting with epsilon (ε) 0.881 to account for multiple comparisons. No main effect of gender with respect to puff duration was observed, F(1, 39) = 0.071, p = 0.791, partial η² = 0.002. After corrections with epsilon (ε) value 0.906, no significant interactions were observed between gender and total puff durations, F(1.813, 70.692) = 2.716, p = 0.078. The main effect of gender was also not significant, F(1, 39) = 0.124, p = 0.727, partial η² = 0.003. Similarly, no significant interactions were found between gender and total interpuff intervals (IPI) (F(1.651, 64.405) = 0.461, p = 0.596) after corrections with epsilon (ε) 0.826.

A statistically significant interaction was found between gender and the mean IPI of various smoking conditions (F(1.557, 60.716) = 5.675, p = 0.010, partial η² = 0.127) after corrections with epsilon (ε) 0.778. Univariate analysis of variance revealed a significant difference in mean IPI during the tobacco cigarette condition was observed between genders, F(1, 39) = 5.323, p = 0.026, η² = 0.120.

### 3.6.3. Subjective Cigarette Craving

A mixed ANOVA was used to investigate various potential interaction effects in the Brief Questionnaire of Smoking Urges (QSU-Brief) data. An epsilon (ε) value of 0.472, as calculated according to Greenhouse-Geisser, was used to correct the analysis as Mauchly’s Test of Sphericity found the assumption of sphericity was violated, χ²(77) = 268.220, p < 0.0005. No significant Condition × Time × Gender interaction (F(5.668, 221.059) = 0.128, p = 0.991, partial η² = 0.003) was found. Similarly, no significant Condition × Gender (F(2.925, 114.071) = 1.048, p = 0.373, partial η² = 0.026), Time × Gender (F(2.148, 83.783) = 0.145, p = 0.879, partial η² = 0.004), and Condition × Time (F(5.668, 221.059) = 1.255, p = 0.281, partial η² = 0.031) interactions were found. Therefore, simple main effects were investigated using repeated measures ANOVA.

Moreover, a one-way MANOVA was conducted and found no statistically significant differences in the total QSU-Brief craving scores between genders (F(12, 28) = 0.424, p = 0.940, Wilk’s Λ = 0.846, partial η² = 0.154).
Table 3.21: Total QSU-Brief scores amongst female participants (n = 22). In comparison to baseline, significant reductions were reported when craving was measured one hour after condition administration (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between experimental conditions in female participants.

<table>
<thead>
<tr>
<th>QSU-Brief Scores</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>58.68 ± 8.64</td>
<td>47.27 ± 9.37</td>
<td>52.14 ± 11.00</td>
<td>55.45 ± 10.43</td>
<td>&lt; 0.0005 (25.299)</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>57.77 ± 7.66</td>
<td>49.32 ± 12.86</td>
<td>52.50 ± 13.26</td>
<td>55.00 ± 11.85</td>
<td>&lt; 0.0005 (12.039)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>59.23 ± 8.09</td>
<td>49.45 ± 14.73</td>
<td>50.64 ± 14.58</td>
<td>53.36 ± 12.72</td>
<td>&lt; 0.0005 (10.679)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>56.64 ± 10.17</td>
<td>47.95 ± 14.88</td>
<td>50.05 ± 14.63</td>
<td>52.50 ± 13.38</td>
<td>&lt; 0.0005 (10.657)</td>
</tr>
</tbody>
</table>

No significant differences were found between the baseline QSU-Brief scores from all the experimental conditions amongst female (F(2.552, 53.598) = 1.502, p = 0.228, partial η² = 0.067) and male (F(2.582, 46.470) = 2.112, p = 0.120, partial η² = 0.105) participants.

Table 3.22: Total QSU-Brief scores amongst male participants (n = 19). In comparison to baseline, significant reductions were reported when craving was measured one hour after condition administration (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between experimental conditions in male participants.

<table>
<thead>
<tr>
<th>QSU-Brief Scores</th>
<th>1-hr (Post Neutral Cues)</th>
<th>1-hr (Post Smoking Cues)</th>
<th>3-hr (Post Neutral Cues)</th>
<th>3-hr (Post Smoking Cues)</th>
<th>p-value (F score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Cigarettes</td>
<td>52.74 ± 13.32</td>
<td>41.68 ± 14.53</td>
<td>46.95 ± 15.58</td>
<td>50.11 ± 13.85</td>
<td>&lt; 0.0005 (17.595)</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>56.21 ± 8.80</td>
<td>46.63 ± 11.30</td>
<td>51.32 ± 10.48</td>
<td>52.11 ± 12.12</td>
<td>0.001 (8.127)</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>56.42 ± 9.43</td>
<td>46.53 ± 14.57</td>
<td>49.05 ± 14.88</td>
<td>51.47 ± 13.71</td>
<td>0.001 (8.227)</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td>55.79 ± 9.25</td>
<td>46.42 ± 14.25</td>
<td>49.05 ± 14.22</td>
<td>52.16 ± 12.58</td>
<td>0.002 (8.253)</td>
</tr>
</tbody>
</table>
Significant differences were observed between QSU-Brief scores at various time points during the tobacco cigarettes condition amongst both female (F(2.820, 59.225) = 25.299, p < 0.0005, partial $\eta^2 = 0.546$) and male (F(2.688, 48.390) = 17.595, p < 0.0005, partial $\eta^2 = 0.494$) participants after corrections with epsilon ($\epsilon$) 0.705 and 0.672 respectively. Amongst female participants, post hoc pairwise comparisons with a Bonferroni adjustment for multiple comparisons identified significant decreases between baseline scores and those reported post-neutral cues (-11.41 (95% CI, -16.25 to -6.57), p < 0.0005) and post-smoking cues (-6.55 (95% CI, -11.92 to -1.17), p = 0.010) presented one hour after the initial smoking condition. In data regarding male participants, a significant reduction was identified between baseline QSU-Brief scores and those reported post-neutral cues presented one hour after smoking (-11.05 (95% CI, -18.08 to -4.02), p = 0.001).

During the e-cigarettes with placebo lozenges condition, significant differences in QSU-Brief scores at various time points were found amongst female (F(2.273, 47.741) = 12.039, p < 0.0005, partial $\eta^2 = 0.364$) and male (F(2.084, 37.504) = 8.127, p = 0.001, partial $\eta^2 = 0.311$) participants after corrections with epsilon ($\epsilon$) 0.568 and 0.521 respectively. Post hoc comparisons revealed significant decreases between baseline measures and those observed post-neutral cues administered one hour after the condition in data regarding female (-8.46 (95% CI, -14.20 to -2.71), p = 0.002) and male (-9.58 (95% CI, -17.86 to -1.30), p = 0.016) participants.

During the e-cigarettes with nicotine lozenges condition, significant differences in QSU-Brief measures were identified amongst female (F(2.044, 42,922) = 10.679, p < 0.0005, partial $\eta^2 = 0.337$) and male (F(1.926, 34,664) = 8.227, p = 0.001, partial $\eta^2 = 0.314$) participants after corrections with epsilon ($\epsilon$) 0.511 and 0.481 respectively. In data regarding female participants, post hoc analysis found significant reductions between baseline measures and those reported post-neutral cues (-9.77 (95% CI, -17.46 to -2.09), p = 0.007) and post-smoking cues (-8.60 (95% CI, -16.02 to -1.16), p = 0.016) administered one hour after the condition. Post hoc comparisons of male participant data revealed a significant decrease between baseline scores and those scored post-neutral cues (-9.90 (95% CI, -18.50 to -1.29), p = 0.017) presented one hour after the condition.

Significant differences in QSU-Brief scores at various time points were observed amongst female (F(1.893, 30.760) = 10.657, p < 0.0005, partial $\eta^2 = 0.337$) and male (F(1.676, 30.171) = 8.253, p = 0.002, partial $\eta^2 = 0.314$) participants, after corrections with epsilon ($\epsilon$) 0.473 and 0.419 respectively, during the lozenges alone condition. Post hoc analysis of female participant data found significant reductions between baseline measures and those obtained post-neutral cues (-8.68 (95% CI, -15.87 to -1.50), p = 0.011) and post-smoking cues (-6.59 (95% CI, -13.17 to -0.14), p = 0.049) administered one hour after the initial condition. In men, baseline scores were found significantly different from those reported post-neutral cues presented one hour after the condition (-9.37 (95% CI, -17.37 to -1.37), p = 0.015).
Cue-induced cravings and withdrawal-induced cravings were evaluated. In females, QSU-Brief scores were significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (4.86 (95% CI, 1.52 to 8.20), p = 0.002). A significant increase was observed between scores reported post-neutral cues one hour after smoking and those reported post-neutral cues three hours after smoking (8.18 (95% CI, 4.63 to 11.74), p < 0.0005). Similarly, in males, QSU-Brief scores were significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes (5.26 (95% CI, 0.10 to 10.43), p = 0.044). A significant difference was detected between craving reported post-neutral cues presented one hour after smoking and those reported post-neutral cues three hours after smoking (8.42 (95% CI, 4.46 to 12.38), < 0.0005).

During the e-cigarettes with placebo lozenges condition, a significant increase were detected between cravings measured post-neutral cues and post-smoking cues administered one hour after the condition in female (3.18 (95% CI, 0.05 to 6.32), p = 0.045) and male (4.68 (95% CI, 0.06 to 9.31), p = 0.046) participants. A significant increase was also observed between craving reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition in female participants (5.68 (95% CI, 1.83 to 9.54), p = 0.001). Conversely, no significant difference was found between craving reported post-neutral cues administered one and three hours after the condition in male participants (5.47 (95% CI, -1.01 to 11.96), p = 0.147).

During the e-cigarettes with nicotine lozenges condition, no significant increases were observed between QSU-Brief scores reported post-neutral cues and post-smoking cues administered one hour after the condition in female (1.18 (95% CI, -1.05 to 3.41), p = 1.000) and male (2.53 (95% CI, -0.23 to 5.29), p = 0.090) participants. Similarly, no significant increases were identified between cravings measured post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition in female (3.91 (95% CI, -1.72 to 9.54), p = 0.409) and male (4.95 (95% CI, -2.05 to 11.94), p = 0.364) participants.

Similarly, during the nicotine lozenges alone condition, no significant differences were detected between craving measured post-neutral cues and post-smoking cues administered one hour after the condition in female (2.09 (95% CI, -0.17 to 4.35), p = 0.085) and male (2.63 (95% CI, -1.27 to 6.53), p = 0.447) participants. However, significant increases were observed between craving reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition in female participants (4.55 (95% CI, 0.55 to 8.54), p = 0.018). No significant differences were observed between post-neutral cues administered one and three hours after the condition in male participants (5.74 (95% CI, -1.49 to 12.96), p = 0.206).

QSU-Brief scores measured at various time points were then subtracted with those reported post-neutral cues administered one hour after the conditions to investigate differences in cue-induced and withdrawal-induced cravings between genders (summarized in Table 3.23).
Table 3.23: Normalized QSU-Brief craving scores by genders. Significant differences in cue-induced craving were found between experimental conditions in female (p = 0.028) and male (p = 0.040) participants. However, no significant differences in withdrawal-induced craving were observed between conditions in both gender groups (p > 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between smoking conditions within each gender group.

<table>
<thead>
<tr>
<th></th>
<th>Normalized Total QSU-Brief Scores</th>
<th></th>
<th></th>
<th></th>
<th>F score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tobacco Cigarettes</td>
<td>E-Cigarettes w Placebo Lozenges</td>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td>Lozenges Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-hr (Post Smoking Cues)</td>
<td>Female</td>
<td>4.86 ± 5.00</td>
<td>3.18 ± 4.69</td>
<td>1.18 ± 3.33</td>
<td>2.09 ± 3.38</td>
<td>3.240</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>5.26 ± 7.04</td>
<td>4.68 ± 6.31</td>
<td>2.53 ± 3.76</td>
<td>2.63 ± 5.32</td>
<td>2.976</td>
</tr>
<tr>
<td>3-hr (Post Neutral Cues)</td>
<td>Female</td>
<td>8.18 ± 5.32</td>
<td>5.68 ± 5.77</td>
<td>3.91 ± 8.42</td>
<td>4.55 ± 5.97</td>
<td>2.005</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>8.42 ± 5.40</td>
<td>5.47 ± 8.85</td>
<td>4.95 ± 9.54</td>
<td>5.74 ± 9.85</td>
<td>1.511</td>
</tr>
<tr>
<td>3-hr (Post Smoking Cues)</td>
<td>Female</td>
<td>10.32 ± 5.78</td>
<td>7.59 ± 6.35</td>
<td>7.05 ± 8.81</td>
<td>7.41 ± 8.16</td>
<td>1.202</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>11.63 ± 7.93</td>
<td>8.80 ± 11.66</td>
<td>7.79 ± 9.54</td>
<td>8.32 ± 10.87</td>
<td>1.324</td>
</tr>
</tbody>
</table>

Cue-induced cravings, evaluated by the normalized scores reported post-smoking cues presented one hour after conditions, were significantly different between various conditions in women (F(3, 120) = 3.240, p = 0.028, partial $\eta^2 = 0.134$) and men (F(3, 120) = 2.976, p = 0.040, partial $\eta^2 = 0.142$). Post hoc analysis with a Bonferroni adjustment detected no significant differences in cue-induced cravings between conditions in men (p > 0.05). However, in women, significantly lower cue-induced cravings during the e-cigarettes with nicotine lozenges condition was detected in comparison to the tobacco cigarette condition (-3.68 (95% CI, -7.11 to -0.25), p = 0.031).

No significant differences in withdrawal-induced cravings were observed in women (F(3, 120) = 2.005, p = 0.122, partial $\eta^2 = 0.087$) and men (F(3, 120) = 1.511, p = 0.222, partial $\eta^2 = 0.077$). Similarly, no significant differences in cravings at the end of each visit, representing compounded cue and withdrawal-induced cravings, were detected between conditions in women (F(3, 120) = 1.202, p = 0.316, $\eta^2 = 0.054$) and men (F(3, 120) = 1.324, p = 0.276, partial $\eta^2 = 0.069$).

When analyzed by gender, the data regarding the Brief Questionnaire of Smoking Urges (QSU-Brief) Factor subscale scores contained outliers. The outliers were kept in the data for analysis since the sources varied. Repeated measures ANOVA used to investigate differences the QSU-Brief Factor 1 and Factor 2 scores, summarized in Table 3.24 and Table 3.25.
Table 3.24: QSU-Brief Factor 1 scores. In comparison to baseline, significant decreases were reported when craving was measured one hour after condition administration (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between experimental conditions within each gender group.

<table>
<thead>
<tr>
<th>QSU-Brief Factor 1 Subscale Scores</th>
<th>F score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco Cigarettes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32.64 ± 2.80</td>
<td>26.50 ± 3.96</td>
</tr>
<tr>
<td>Male</td>
<td>29.79 ± 5.36</td>
<td>23.58 ± 7.50</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32.18 ± 2.68</td>
<td>28.09 ± 6.00</td>
</tr>
<tr>
<td>Male</td>
<td>31.74 ± 2.40</td>
<td>27.58 ± 5.40</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32.64 ± 2.70</td>
<td>27.36 ± 7.51</td>
</tr>
<tr>
<td>Male</td>
<td>31.16 ± 2.87</td>
<td>25.84 ± 7.51</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31.23 ± 3.64</td>
<td>26.73 ± 7.57</td>
</tr>
<tr>
<td>Male</td>
<td>30.79 ± 3.95</td>
<td>26.63 ± 7.26</td>
</tr>
</tbody>
</table>

No significant differences were found between the baseline QSU-Brief Factor 1 subscale scores from all the experimental conditions in women (F(2.106, 44.217) = 2.268, p = 0.113, partial η² = 0.097) and men (F(1.993, 35.876) = 2.095, p = 0.138, partial η² = 0.104).

In women, significant differences were observed between QSU-Brief Factor 1 subscale scores at various time points during the tobacco cigarettes condition (F(2.880, 60.482) = 25.503, p < 0.0005, partial η² = 0.548) after correcting with epsilon (ε) 0.720. Post hoc pairwise comparisons with a Bonferroni adjustment for multiple comparisons found significant reductions between baseline scores and those measured post-neutral cues (-6.14 (95% CI, -8.87 to -3.41), p < 0.0005) and post-smoking cues (-3.14 (95% CI, -5.93 to -0.34), p = 0.020) presented one hour after smoking. Similarly, in men, significant differences were found between Factor 1 scores during the tobacco cigarettes condition (F(2.670, 46.920) = 15.245, p < 0.0005, partial η² = 0.459) after epsilon (ε) 0.652 corrections. Post hoc pairwise comparisons with a Bonferroni adjustment identified significant decrease between baseline scores and those measured post-neutral cues (-6.21 (95% CI, -10.21 to -2.21), p = 0.001) administered one hour after smoking.
Significant differences were found between Factor 1 subscale scores during the e-cigarettes with placebo lozenges condition in women \(F(2.602, 54.643) = 11.490, p < 0.0005, \text{ partial } \eta^2 = 0.354\) and men \(F(2.219, 39.937) = 6.413, p = 0.003, \text{ partial } \eta^2 = 0.263\) after correcting with epsilon (\(\epsilon\)) values 0.651 and 0.555 respectively. Post hoc comparisons revealed significant reductions between baseline scores and those obtained post-neutral cues administered one hour after the condition in women (-4.09 (95% CI, -7.03 to -1.15), \(p = 0.003\)) and men (-4.16 (95% CI, -7.81 to -0.51), \(p = 0.019\)).

During the e-cigarettes with nicotine lozenges visit, significant differences were observed in scores of women \(F(1.546, 32.476) = 7.770, p = 0.003, \text{ partial } \eta^2 = 0.270\) and men \(F(2.040, 36.716) = 7.985, p = 0.001, \text{ partial } \eta^2 = 0.307\) after correcting with epsilon (\(\epsilon\)) values 0.387 and 0.510 respectively. Post hoc comparisons revealed a significant decrease between only baseline scores and those obtained post-neutral cues presented one hour after the condition in women (-5.27 (95% CI, -10.09 to -0.46), \(p = 0.025\)) and men (-5.32 (95% CI, -10.00 to -0.63), \(p = 0.019\)).

During the lozenges alone condition, significant differences are again found in scores from women \(F(1.615, 33.914) = 8.374, p = 0.002, \text{ partial } \eta^2 = 0.285\) and men \(F(1.691, 30.436) = 5.518, p = 0.012, \text{ partial } \eta^2 = 0.235\) after correcting with epsilon (\(\epsilon\)) values 0.404 and 0.423 respectively. However, in both gender groups, post hoc analysis found no significant differences between scores reported at baseline and those measured at subsequent time points (\(p > 0.05\)).

Cue-induced cravings and withdrawal-induced cravings were investigated. QSU-Brief Factor 1 subscale scores were significantly increased between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes in female (3.00 (95% CI, 1.00 to 5.00), \(p = 0.001\)) and male (2.84 (95% CI, 0.20 to 5.49), \(p = 0.030\)) participants. Significant increases were also observed between scores reported post-neutral cues presented one hour after smoking and those reported post-neutral cues three hours after smoking in female (4.41 (95% CI, 2.55 to 6.27), \(p < 0.0005\)) and male (4.63 (95% CI, 2.53 to 6.74), \(p < 0.0005\)) participants.

No significant changes were detected between QSU-Brief Factor 1 scores measured post-neutral cues and post-smoking cues administered one hour after using e-cigarettes with placebo lozenges in female (1.50 (95% CI, -0.32 to 3.32), \(p = 0.173\)) and male (2.21 (95% CI, -0.19 to 4.61), \(p = 0.087\)) participants. In male participants, no significant change in craving was observed post-neutral cues presented one hour after condition and post-neutral presented three hours after the condition (2.47 (95% CI, -0.83 to 5.78), \(p = 0.277\)). However, a significant increase was observed between craving reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition in female participants (2.73 (95% CI, 0.61 to 4.84), \(p = 0.006\)).
During the e-cigarettes with nicotine lozenges condition, no significant increases were observed between QSU-Brief scores reported post-neutral cues and post-smoking cues administered one hour after the condition in female participants (0.68 (95% CI, -0.60 to 1.96), p = 1.000). Similarly, no significant difference was identified between craving measured post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition (2.41 (95% CI, -1.52 to 6.34), p = 0.682). In male participants, significant increases in craving were observed between scores reported post-neutral and post-smoking cues administered one hour after the condition (1.32 (95% CI, 0.02 to 2.61), p = 0.045). However, no significant changes were observed when compared with neutral-cues administered three hours after the condition (2.74 (95% CI, -0.68 to 6.15), p = 0.195).

During the nicotine lozenges alone condition, significant increases were detected between craving measured post-neutral cues and post-smoking cues administered one hour after the condition in female participants (1.36 (95% CI, 0.03 to 2.69), p = 0.042). Significant differences were also detected between craving reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition (3.00 (95% CI, 0.59 to 5.41), p = 0.008). Conversely, in male participants, no significant difference was found between Factor 1 subscale scores reported post-neutral and post-smoking cues presented one hour after the condition (1.32 (95% CI, -0.99 to 3.62), p = 0.849). No significant change was observed between craving measured post-neutral cues administered one and three hours after the initial condition (2.79 (95% CI, -1.37 to 6.95), p = 0.460).
Table 3.25: QSU-Brief Factor 2 scores. In comparison to baseline, significant decreases were reported when craving was measured one hour after condition administration (p < 0.05). Values are expressed as mean ± standard deviation (SD). Analysis was conducted using the repeated measures ANOVA and p-values shown reflect differences between experimental conditions within each gender group.

<table>
<thead>
<tr>
<th></th>
<th>QSU-Brief Factor 2 Subscale Scores</th>
<th>F</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1-hr (Post Neutral Cues)</td>
<td>1-hr (Post Smoking Cues)</td>
</tr>
<tr>
<td>Tobacco Cigarettes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26.05 ± 6.99</td>
<td>20.77 ± 6.20</td>
<td>22.64 ± 7.84</td>
</tr>
<tr>
<td>Male</td>
<td>22.95 ± 8.95</td>
<td>18.11 ± 8.31</td>
<td>20.53 ± 9.06</td>
</tr>
<tr>
<td>E-Cigarettes w Placebo Lozenges</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25.59 ± 5.82</td>
<td>21.23 ± 7.74</td>
<td>22.91 ± 8.32</td>
</tr>
<tr>
<td>Male</td>
<td>24.47 ± 7.63</td>
<td>19.05 ± 7.40</td>
<td>21.53 ± 7.46</td>
</tr>
<tr>
<td>E-Cigarettes w Nicotine Lozenges</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26.41 ± 6.24</td>
<td>22.09 ± 8.11</td>
<td>22.59 ± 7.91</td>
</tr>
<tr>
<td>Male</td>
<td>25.16 ± 7.30</td>
<td>20.68 ± 7.73</td>
<td>21.89 ± 8.49</td>
</tr>
<tr>
<td>Lozenges Alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25.41 ± 7.14</td>
<td>21.23 ± 8.09</td>
<td>21.95 ± 8.32</td>
</tr>
<tr>
<td>Male</td>
<td>25.00 ± 5.87</td>
<td>19.79 ± 8.10</td>
<td>21.11 ± 8.54</td>
</tr>
</tbody>
</table>

No significant differences were found between the baseline QSU-Brief Factor 2 subscale scores from all the experimental conditions in women (F(2.993, 62.849) = 0.534, p = 0.661, partial η² = 0.025) and men (F(2.769, 49.834) = 1.628, p = 0.198, partial η² = 0.083).

In women, significant differences were observed between QSU-Brief Factor 2 subscale scores at various time points during the tobacco cigarettes condition F(2.829, 59.410) = 16.089, p < 0.0005, partial η² = 0.434) after correcting with epsilon (ε) 0.707. Post hoc pairwise comparisons with a Bonferroni adjustment revealed significant differences between baseline scores and those measured post-neutral cues (-5.27 (95% CI, -8.11 to -2.44), p < 0.0005) and post-smoking cues (-3.41 (95% CI, -6.41 to -0.41), p = 0.018) presented one hour after smoking. In men, significant differences were also found between scores during the tobacco cigarettes condition F(2.529, 45.524) = 15.117, p < 0.0005, partial η² = 0.456) after correcting with epsilon (ε) 0.632. Post hoc comparisons found a significant reduction between baseline scores and those measured post-neutral cues administered one hour after smoking (-4.84 (95% CI, -8.50 to -1.19), p = 0.005).
During the e-cigarettes with placebo lozenges condition, significant differences were found between Factor 2 scores in women (F(2.340, 49.145) = 8.043, p = 0.001, partial $\eta^2 = 0.277$) and men (F(2.214, 39.857) = 8.124, p = 0.001, partial $\eta^2 = 0.311$) after correcting with epsilon ($\epsilon$) values 0.585 and 0.554 respectively. Post hoc comparison revealed significant differences between baseline scores and those obtained post-neutral cues administered one hour after the condition in women (-4.36 (95% CI, -7.60 to -1.13), p = 0.004) and men (-5.42 (95% CI, -10.24 to -0.60), p = 0.021).

Significant differences were observed in scores of women (F(2.421, 50.831) = 8.890, p < 0.0005, partial $\eta^2 = 0.320$) and men (F(1.898, 34.167) = 5.955, p = 0.007, partial $\eta^2 = 0.249$), after correcting with epsilon ($\epsilon$) values 0.605 and 0.475 respectively, during the e-cigarettes with nicotine lozenges condition. In women, post hoc analyses revealed significant reductions between baseline reports and those obtained post-neutral cues (-4.32 (95% CI, -7.98 to -0.66), p = 0.013) and post-smoking cues (-3.82 (95% CI, -7.08 to -0.55), p = 0.014) presented one hour after the condition. However, in men, no significant differences were observed between baseline scores and those reported at subsequent time points (p > 0.05).

During the lozenge alone condition, significant differences are also observed in Factor 2 subscale scores from women (F(2.394, 50.269) = 9.889, p < 0.0005, partial $\eta^2 = 0.320$) and men (F(2.094, 37.691) = 9.406, p < 0.0005, partial $\eta^2 = 0.343$), after correcting with epsilon ($\epsilon$) values 0.598 and 0.523 respectively. In men, post hoc analysis identified significant reductions between only baseline scores and those obtained post-neutral cues (-5.21 (95% CI, -9.10 to -1.32), p = 0.005) and post-smoking cues (-3.90 (95% CI, -7.60 to -0.19), p = 0.035) presented one hour after the condition. However, in women, significant differences were observed between baseline scores and those reported post-neutral cues (-4.18 (95% CI, -7.42 to -0.94), p = 0.006) and post-smoking cues (-3.46 (95% CI, -6.42 to -0.49), p = 0.015) administered one hour later, as well as between baseline scores and those reported post-neutral cues administered three hours after the initial condition (-2.64 (95% CI, -5.16 to -0.11), p = 0.036).

Cue-induced cravings and withdrawal-induced cravings were investigated. QSU-Brief Factor 2 subscale scores were not significantly different between post-neutral and post-smoking cues presented one hour after smoking tobacco cigarettes in female (1.86 (95% CI, -0.15 to 3.88), p = 0.085) and male (2.42 (95% CI, -0.63 to 5.47), p = 0.205) participants. Scores reported post-neutral cues presented one hour after smoking and those reported post-neutral cues three hours after smoking were significantly increased in female (3.77 (95% CI, 1.43 to 6.12), p = 0.001) and male (3.79 (95% CI, 1.39 to 6.19), p = 0.001) participants.

During the e-cigarettes with placebo lozenges condition, no significant changes were detected between QSU-Brief Factor 2 scores measured post-neutral cues and post-smoking cues administered one hour after the condition in female participants (1.68 (95% CI, -0.22 to 3.59), p = 0.116). A significant increase in craving was observed between assessments post-neutral cues presented one and three hours after
the condition (2.96 (95% CI, 0.19 to 5.72), p = 0.030). Conversely, in male participants, a significant increase in craving was observed between scores reported post-neutral cues and post-smoking cues administered one hour after the condition (2.47 (95% CI, 0.11 to 4.84), p = 0.036). However, no significant change was observed between craving reported post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition (3.00 (95% CI, -0.47 to 6.47), p = 0.129).

During the e-cigarettes with nicotine lozenges condition, no significant differences were found between QSU-Brief scores reported post-neutral cues and post-smoking cues administered one hour after the condition in female (0.50 (95% CI, -1.15 to 2.15), p = 1.000) and male (1.21 (95% CI, -0.72 to 3.14), p = 0.607) participants. Similarly, no significant differences were identified between craving measured post-neutral cues presented one hour after the condition and post-neutral cues presented three hours after the condition in female (1.50 (95% CI, -0.84 to 3.84), p = 0.575) and male (2.21 (95% CI, -1.70 to 6.12), p = 0.873) participants.

No significant changes were detected between craving measured post-neutral cues and post-smoking cues administered one hour after using nicotine lozenges alone in female (0.73 (95% CI, -0.51 to 1.97), p = 0.803) and male (1.32 (95% CI, -0.67 to 3.30), p = 0.484) participants. No significant difference was found between Factor 2 scores measured post-neutral cues administered one and three hours after the initial condition in female (1.55 (95% CI, -0.39 to 3.48), p = 0.204) and male (2.95 (95% CI, -0.68 to 6.58), p = 0.183) participants.

3.7. Summary of Adverse Events

No statistically significant differences were observed between the rates of various adverse events reported in each experimental condition (p > 0.05). However, it should be noted that the most common reported adverse events across all conditions were anxiety, fatigue, dry throat, dry mouth, and drowsiness.
3.8. **Physiological Assessments**

3.8.1. **Carbon Monoxide**

Expired carbon monoxide levels are summarized in Table 3.26. No significant differences were found between the baseline expired carbon monoxide measures from all the experimental conditions (F(2.934, 117.346) = 1.557, p = 0.205).

During the tobacco cigarette condition, significant increases in expired carbon monoxide (CO) levels were observed between baseline and end-of-visit assessments (1.63 (95% CI, 0.97 to 2.30), p < 0.0005). Significant decreases in expired carbon monoxide levels were found between baseline and end-of-visit measurements during the e-cigarettes with placebo lozenges (-1.66 (95% CI, -2.13 to -1.19), p < 0.0005), e-cigarettes with nicotine lozenges (-2.22 (95% CI, -2.80 to -1.64), p < 0.0005), and lozenges alone (-1.51 (95% CI, -2.03 to -0.99), p < 0.0005) conditions.

**Table 3.26:** Expired Carbon Monoxide (CO). Significant reduction in CO was observed during both e-cigarettes and nicotine lozenges alone conditions. Smoking tobacco cigarettes significantly increased CO. Values are expressed as mean ± standard deviation (SD). P-values shown reflect differences in expired CO measured at the start and end of study visits.

<table>
<thead>
<tr>
<th>Expired Carbon Monoxide (ppm)</th>
<th>Start of Visit</th>
<th>End of Visit</th>
<th>F score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tobacco Cigarettes</strong></td>
<td>5.98 ± 3.61</td>
<td>7.61 ± 3.84</td>
<td>24.397</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td><strong>E-Cigarettes with Placebo Lozenges</strong></td>
<td>6.39 ± 3.62</td>
<td>4.73 ± 2.80</td>
<td>51.723</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td><strong>E-Cigarettes with Nicotine Lozenges</strong></td>
<td>6.66 ± 3.53</td>
<td>4.44 ± 2.34</td>
<td>60.733</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td><strong>Lozenges Alone</strong></td>
<td>6.07 ± 3.54</td>
<td>4.56 ± 2.47</td>
<td>34.646</td>
<td>&lt; 0.0005</td>
</tr>
</tbody>
</table>

3.8.2. **Heart Rate and Blood Pressure**

Measures of heart rate and blood pressure are summarized in Table 3.27 and Table 3.28 respectively. No significant differences were found between the baseline heart rate measures from all the experimental conditions (F(3, 120) = 1.081, p = 0.360). Significant decreases were observed in heart rate between baseline and end-of-visit assessments during the tobacco cigarettes condition (-1.73 (95% CI, -3.28 to -0.19) bpm, p = 0.029) and e-cigarettes with placebo lozenges condition (-4.61 (95% CI, -5.92 to -3.30) bpm, p < 0.0005). No significant differences were observed in heart rate levels during the e-cigarettes with nicotine lozenges and lozenges alone conditions.
A significant increase in systolic pressure was measured during the lozenges alone condition between basement and end-of-visit assessments (2.732 (95% CI, 1.17 to 4.30) mm Hg, p = 0.001). No significant differences were observed between systolic pressure measured at baseline and end-of-visit during the tobacco cigarettes (0.68 (95% CI, -1.15 to 2.52) mm Hg, p = 0.456), e-cigarettes with placebo lozenges (-0.68 (95% CI, -2.18 to 0.82) mm Hg, p = 0.362), and e-cigarettes with nicotine lozenges conditions (1.46 (95% CI, -0.28 to 3.20) mm Hg, p = 0.097).

Significant increases in diastolic pressure were observed between baseline and end-of-visit assessments during the e-cigarettes with nicotine lozenges (3.32 (95% CI, 1.53 to 5.11) mm Hg, p = 0.001) and lozenges alone conditions (4.54 (95% CI, 2.98 to 6.10) mm Hg, p < 0.0005). No significant differences in diastolic measures were observed between baseline and end-of-visit assessments during the tobacco cigarettes (1.12 (95% CI, -0.33 to 2.58) mm Hg, p = 0.127) and e-cigarettes with placebo lozenges (0.10 (95% CI, -1.69 to 1.89) mm Hg, p = 0.913) conditions.
Table 3.28: Blood Pressure. Significant increases in systolic pressure were observed during the nicotine lozenges alone condition. Values are expressed as mean ± standard deviation (SD). P-values shown reflect differences in blood pressure measured at the start and end of study visits.

<table>
<thead>
<tr>
<th>Blood Pressure (mm Hg)</th>
<th>Start of Visit</th>
<th>End of Visit</th>
<th>F score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tobacco Cigarettes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>117.32 ± 12.39</td>
<td>118.00 ± 12.85</td>
<td>0.567</td>
<td>0.456</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70.68 ± 10.91</td>
<td>71.80 ± 11.99</td>
<td>2.433</td>
<td>0.127</td>
</tr>
<tr>
<td><strong>E-Cigarettes with Placebo Lozenges</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115.66 ± 14.28</td>
<td>114.98 ± 13.15</td>
<td>0.849</td>
<td>0.362</td>
</tr>
<tr>
<td>Diastolic</td>
<td>68.34 ± 10.57</td>
<td>68.44 ± 11.26</td>
<td>0.012</td>
<td>0.913</td>
</tr>
<tr>
<td><strong>E-Cigarettes with Nicotine Lozenges</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>114.44 ± 13.10</td>
<td>115.90 ± 11.72</td>
<td>2.888</td>
<td>0.097</td>
</tr>
<tr>
<td>Diastolic</td>
<td>67.80 ± 9.87</td>
<td>71.12 ± 10.96</td>
<td>14.044</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Lozenges Alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>113.61 ± 12.34</td>
<td>116.34 ± 11.86</td>
<td>12.436</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Diastolic</td>
<td>68.29 ± 11.13</td>
<td>72.83 ± 11.08</td>
<td>34.575</td>
<td>&lt; 0.0005</td>
</tr>
</tbody>
</table>

3.9. Effect of Different Nicotine Lozenge Brands

As mentioned in the Methods section (Section 2.6.1), two brands of mini nicotine lozenges were used in the current study due to stock shortages. The first 39 participants (2 of whom withdrew from the study) received Nicorette® mini nicotine lozenges while the remaining 4 participants received Life Brand mini nicotine lozenges.

A mixed ANOVA was used to investigate various potential interaction effects in the QSU-Brief data. An epsilon (ε) value of 0.471, as calculated according to Greenhouse-Geisser, was used to correct the analysis as Mauchly’s Test of Sphericity found the assumption of sphericity was violated, $\chi^2(77) = 267.977, p < 0.0005$. No significant Condition × Time × Gender interaction (F(5.648, 220.283) = 0.422, p = 0.854, partial $\eta^2 = 0.011$) was found. Similarly, no significant Condition × Lozenge (F(2.903, 113.221) = 0.083, p = 0.966, partial $\eta^2 = 0.002$), Time × Lozenge (F(2.110, 82.279) = 1.223, p = 0.301, partial $\eta^2 = 0.030$), and Condition × Time (F(5.648, 220.283) = 0.508, p = 0.792, partial $\eta^2 = 0.013$) interactions were found.
4. Discussion

This study is one of few to investigate whether non-nicotinic e-cigarettes may reduce cigarette craving by satiating behavioral cues, and the only e-cigarette study to use a cue-reactivity paradigm. The primary findings of the study were that tobacco cigarettes most significantly reduced cravings one hour after administering the experimental condition, while non-nicotinic e-cigarettes used with nicotine lozenges were most effective in attenuating cue-induced and withdrawal-induced cravings over time. Moreover, e-cigarettes with nicotine lozenges were most effective in sustaining reduced cigarette cravings in comparison to smoking tobacco cigarettes, e-cigarettes with placebo lozenges, or using nicotine lozenges alone.

To date, few studies have investigated the influence of smoking behavior on cigarette craving and nicotine withdrawal symptoms, independent from nicotine administration. One group investigated the effect of sensorimotor cues on smoking satiation in 18 smokers randomized to receive intravenous nicotine with or without concurrently smoking denicotinized cigarettes (Rose, Behm, Westman, Bates, & Salley, 2003). Similar to the findings in the current study, investigators reported denicotinized cigarettes produced a considerable degree of satiation, assessed by reduced tobacco cigarette smoking. Moreover, a smaller effect was observed as a result of intravenous nicotine administration. However, the study had some significant limitations. Puffs from the experimental conditions were administered to participants by a spirometric apparatus. While investigators individualized smoke patterns and nicotine delivery following an ad libitum smoking visit, the puffs delivered by the apparatus may not fully reflect usual smoking behavior. Moreover, intravenous nicotine delivery does not replicate effects of pulmonary nicotine delivery. In the current study, the design allowed participants to use e-cigarettes ad libitum for 5 minutes so that smoking behavioral would be better simulated. Moreover, nicotine was delivered through lozenges and participants were not encumbered or discomforted by an intravenous line.

Several studies have investigated the effects of e-cigarettes on subjective craving and withdrawal symptoms. An earlier study aiming to evaluate nicotine delivery and craving suppression recruited 16 e-cigarette naïve smokers to smoke tobacco cigarettes, two kinds of 16mg nicotine e-cigarettes, and an unlit tobacco cigarette in a Latin-Square design (Eissenberg, 2010). Participants smoked 10 puffs twice with a 60-minute rest period. Both e-cigarettes reduced cigarette cravings less effectively than smoking tobacco cigarettes. A subsequent clinical laboratory study following the similar methodological procedures recruited 32 e-cigarette naïve users and reported e-cigarettes to significantly decrease cigarette craving and some withdrawal symptoms at several time points (Vansickel et al., 2010). However, a limitation of both studies was that participants were restricted to taking 10 puffs per smoking period and results may not reflect effects of unrestricted use. Moreover, the brief period of exposure limited participants from gaining experiences from the devices. As such, results cannot be generalized to users with more experience or regular e-cigarette users. In the current study, participants were given 5 minutes to use e-cigarette ad libitum, providing them an opportunity to gain experience using the
devices. Our analysis of smoking topography during the 5-minute smoking period revealed participants smoked an average of one cigarette during the tobacco cigarette condition and took an average of 20 puffs during e-cigarette conditions, suggesting the 10-puff condition in previous studies may not be sufficient to reflect regular use.

Another study investigated the short-term effects of e-cigarettes on the desire to smoke and withdrawal symptoms and the pharmacokinetics of nicotine (C. Bullen et al., 2010). Forty overnight smoking abstinent e-cigarette naïve smokers were randomized use a 16mg nicotine e-cigarette, a 0mg nicotine e-cigarette, a nicotine inhaler, or smoke tobacco cigarettes for one hour. Measures of desire to smoke and withdrawal symptoms were measured before and at various time points after smoking the assigned condition. In keeping with our own findings, investigators found tobacco cigarettes to most significantly and rapidly reduce the desire to smoke. Reductions in desire to smoke achieved from using 16mg nicotine e-cigarettes and nicotine inhalers were comparable at various time points. While participants using 16mg nicotine e-cigarettes reported greater reductions in their desire to smoke in comparison to those using 0mg nicotine e-cigarettes, differences between the two conditions were not significant. Similarly, no significant differences in desire to smoke were reported between 0mg nicotine e-cigarettes and nicotine inhaler conditions. Moreover, while smoking tobacco cigarettes reduced withdrawal ratings more than other conditions, investigators found no differences in withdrawal symptoms between the 16mg nicotine e-cigarette and nicotine inhaler conditions. Contrary to the findings of the current study, behavioral cues and nicotine administration were not found to have an additive effect on cigarette craving. However, the target sample size of 48 participants was not achieved and the study was not powered to detect significant differences between 16mg nicotine e-cigarettes and nicotine inhalers. Moreover, the study investigated changes in the desire to smoke following a single brief smoking session that may not reflect effects of prolonged use.

Similarly, 86 e-cigarette naïve smokers were recruited and randomized to use either 18mg nicotine e-cigarettes or 0mg nicotine e-cigarettes, or to hold an e-cigarette cigarette for 5 minutes (Dawkins et al., 2012). Consistent with our findings, the desire to smoke was significantly reduced in both using e-cigarette conditions in comparison to holding e-cigarettes and greater reductions were observed in the 18mg nicotine e-cigarette condition in comparison to placebo. However, since participants were smoking abstinent for only one hour prior to the study visit, more robust effects may be observed with a longer period of abstinence. Moreover, all studies mentioned recruited e-cigarette naïve users; however, experience with e-cigarettes has been found to affect e-cigarette use and acceptability (Etter & Bullen, 2011b; Vansickel & Eissenberg, 2013).

A study involving 14 experienced e-cigarette users evaluated the effects of using 18mg nicotine e-cigarettes on the urge to smoke, withdrawal symptoms, and blood nicotine concentrations (Dawkins & Corcoran, 2013) after overnight smoking abstinence. Participants were asked to take 10 puffs, followed by an hour break, and ad libitum smoking for one hour. Urges to smoke were significantly reduced
following both the 10-puff and ad libitum smoking periods. However, no control group using 0mg nicotine e-cigarettes was included in the study design for comparison of effects. To evaluate nicotine delivery and subjective effects, 8 experienced e-cigarette users were recruited and were instructed to use their preferred e-cigarettes for 10 puffs, followed by 15-minute break and a 60-minute ad libitum smoking period (Vansickle & Eissenberg, 2013). QSU factor 1 scores, investigating intention to smoke, and negative affects were significantly reduced. However, a limitation of the study was the lack of a control group using non-nicotinic e-cigarettes.

4.1. Smoking Topography

4.1.1. Order Effects

Current literature speculates naïve e-cigarette users may initially follow a learning curve, during which users modify their smoking topography to account for differences between e-cigarettes and tobacco cigarettes. In the current study, participants were not given an opportunity to become familiar with the use of e-cigarettes prior to the first e-cigarette smoking condition. As a result, a partial Latin Square randomization design was used to account for potential order effects. Smoking topography was assessed through video recordings, which have been found to produce similar results to computerized mouthpiece devices (Blank, Disharoon, & Eissenberg, 2009).

While not significant, the mean puff duration measured during the second visit in which e-cigarettes were used was longer than that of the first e-cigarette visit. Moreover, significantly more puffs were taken during the second e-cigarette visit in comparison to the first. Conversely, the mean IPI observed during the second e-cigarette visit was significantly shorter than that of the first e-cigarette visit.

The cumulative number of puffs taken until each minute mark was tabulated to evaluate smoking trends throughout the 5-minute smoking period. The more in-depth analysis of smoking patterns revealed participants consistently took significantly more puffs throughout the 5-minute smoking period during both their e-cigarette visits in comparison to the tobacco cigarette visit. Significantly more puffs were taken cumulatively at the 1-minute, 2-minute, and 3-minute time points during the second e-cigarette visit in comparison to the first e-cigarette visit. Moreover, differences between the cumulative numbers of puffs taken observed during the first and second e-cigarette visits neared significance at the 4-minute and 5-minute marks.

These findings are consistent with those seen in previous studies (Farsalinos, Romagna, et al., 2013b; Lee et al., 2015). In those studies, as e-cigarette users gained experience, they took longer puffs. Similarly, e-cigarette users have been found to have shorter IPIs as they gain experience (Farsalinos, Romagna, et al., 2013b). Investigators of that study suggested the shorter IPIs may have been observed since longer inhalation time is associated the less vapor exhaled. As such, e-cigarette users may reduce their IPIs to produce more visible vapor upon exhalation to mimic cigarette smoke exhalation.
When a similar analysis was conducted to investigate potential differences in smoking topography under various conditions, the cumulative number of puffs taken until each minute mark during both the e-cigarette with placebo lozenge and e-cigarette with nicotine lozenge conditions were significantly higher than those during the tobacco cigarette condition. However, no significant differences in the cumulative puff numbers were found between the e-cigarette with nicotine lozenge and e-cigarette with placebo lozenge conditions across time points. These findings suggest the partial Latin-Square randomization was effective in counter balancing the order effects on smoking topography.

4.1.2. **Puff Duration and Interpuff Interval (IPI)**

As previously mentioned, significantly fewer puffs were taken while participants smoked tobacco cigarettes in comparison to the number of puffs taken while using e-cigarettes with nicotine lozenges and e-cigarettes with placebo lozenges.

The total and mean puff durations significantly increased during both e-cigarette conditions in comparison smoking tobacco cigarettes. This finding is congruent with previous studies reporting e-cigarette users to take more and longer puffs in comparison to smoking tobacco cigarettes (Farsalinos, Romagna, et al., 2013b; Lee et al., 2015).

The mean IPI significantly decreased during e-cigarettes in comparison to tobacco cigarettes. These results are consistent to findings of a previous study reporting both experienced and naïve e-cigarette used to have lower inhalation times and IPIs (Farsalinos, Romagna, et al., 2013b). Interestingly, while the mean IPI was lower when using e-cigarettes, the total IPI was not significantly different from that when smoking tobacco cigarettes. Despite the shorter mean IPI, since most puffs were taken using e-cigarettes, a similar amount of total non-smoking time was observed between all smoking conditions.

No significant differences in puff topography were observed between using e-cigarettes with nicotine lozenges and e-cigarettes with placebo lozenges. However, it should be noted that in comparison to using e-cigarettes with placebo lozenges, the total and mean puff durations were shorter while using e-cigarettes with nicotine lozenges. This may be a result of nicotine delivery from e-cigarettes such that experienced users learn to use e-cigarettes more intensively and achieve greater plasma nicotine concentrations (Dawkins & Corcoran, 2013; Etter & Bullen, 2011b). However, since participants do not receive nicotine during the e-cigarettes with placebo lozenges condition, they may puff more intensively in an attempt to derive nicotine from the devices.

Smoking topography assessed in the current investigation is consistent with findings from previous studies such that e-cigarette users learn to puff devices more intensively with experience by increasing the number of puffs taken and puff duration and decreasing IPI.
4.2. **Subjective Cigarette Craving**

4.2.1. **Acute Cigarette Craving Reduction**

Using a visual analogue scale (VAS), participants were asked to score five phrases regarding cigarette craving on a scale from 1 to 100. Phrases included, “I have a desire for cigarettes right now”, “If possible, I would smoke a cigarette right now”, “All I want right now is a cigarette”, “I have an urge for cigarettes”, and “I crave cigarettes right now”. Cigarette cravings were also assessed using the QSU-Brief.

When craving was assessed by the VAS one hour following administration of the conditions, smoking tobacco cigarettes most significantly reduced cigarette craving, following by using e-cigarettes with nicotine lozenges, taking nicotine lozenges alone, and using e-cigarettes with placebo lozenges. While no significant differences were observed between conditions following a Bonferroni adjustment, similar results were observed when craving was measured by the total QSU-Brief, as well as the Factor 1 and Factor 2 subscales. These findings are consistent with the study hypothesis that craving reduction is nicotine dose-dependent and smoking tobacco cigarettes will most effectively reduce craving since cigarettes produce higher peak plasma nicotine concentrations than nicotine lozenges (Benowitz, 1988; Choi, Dresler, Norton, & Strahs, 2003). Moreover, nicotine from cigarette smoke delivered through the pulmonary route is absorbed more rapidly than that from lozenges. Similarly, despite receiving identical doses of nicotine in both conditions, the current findings suggest e-cigarettes with nicotine lozenges to be more effective in reducing craving in comparison to taking nicotine lozenges alone. Such findings are similar to observations previously made in a study investigating the nicotinic and non-nicotinic components of cigarette smoking (Rose et al., 2000). Investigators reported that sensorimotor cues and nicotine administration independently reduce craving and the combination of sensorimotor cues and nicotine delivery produced the greatest effects.

Furthermore, the relative decreases in craving observed in this study were similar to reductions in the cravings and desire and urge to smoke observed in previous trials. One study observed significant reductions in the desire to smoke after using nicotinic e-cigarettes and reductions were also not as great as those after smoking tobacco cigarettes (C. Bullen et al., 2010). However, the trial assessed desire to smoking using the Minnesota Nicotine Withdrawal Scale (MNWS) and direct comparisons to the findings of current study cannot be made. Similarly, cigarette cravings as measured by the QSU-Brief and VAS has been found to be significantly reduced following acute administration of 18mg nicotine e-cigarettes (Vansickel et al., 2012). However, in both studies mentioned, nicotinic e-cigarettes were used as opposed to the non-nicotinic e-cigarettes with nicotine lozenges condition in the current study; therefore direct comparisons cannot be made.

More importantly, the significant decrease in acute craving during the e-cigarettes with placebo lozenges condition is consistent with previous findings using nicotinic e-cigarettes and placebo e-cigarettes for 5 minutes reduces the desire to smoke (Dawkins et al., 2012). However, this study only investigated
effects observed 5 and 20 minutes after smoking while the current study evaluated craving one hour after the administration of conditions.

Nonetheless, these results suggest behavioral cues, as demonstrated by the e-cigarettes with placebo lozenges condition, and nicotine administration, as demonstrated by the nicotine lozenges alone condition, both influence cigarette craving. Moreover, when administered in combination, effects on acute cigarette craving may be additive.

4.2.2. **Cue-Induced Cravings**

The VAS and QSU-Factor 2 scores report significant cue-induced cravings during the tobacco cigarettes, e-cigarettes with placebo lozenges, and nicotine lozenges conditions while e-cigarettes with nicotine lozenges successfully attenuated cue-induced cravings, assessed post-smoking cues presented one hour after conditions. In contrast, the total QSU-Brief and Factor 1 subscales found significant cue-induced cravings during all conditions. However, in both craving measures, smoking tobacco cigarettes resulted in the greatest cue-induced craving. Smoking tobacco cigarettes may have had a nicotine priming effect as suggested by animal self-administration reinstatement studies. One group investigated the effect of priming injections of nicotine on reinstatement of nicotine-seeking behaviors in rats (Shaham, Adamson, Grocki, & Corrigall, 1997). Animals were first trained to self-administer nicotine. Substituting nicotine with saline then resulted extinction of behavior. Various doses of nicotine were then administered either subcutaneously (150µg/kg and 300µg/kg) or intravenously (30µg/kg and 60µg/kg) while saline injections acted as controls. Investigators reported acute re-exposure (priming) injections of nicotine reinstated self-administration behavior in rats after prolonged extinction periods regardless of dose and route of administration. These findings suggest, in comparison to more gradual nicotine delivery from lozenges (Choi et al., 2003) during the other nicotinic conditions, acute rapid administration of nicotine from tobacco cigarette smoke may cause participants to experience greater increases in craving after presentation of smoking cues.

Using e-cigarettes with placebo lozenges and taking nicotine lozenges alone produced very similar effects while combining e-cigarettes with nicotine lozenges seemed to produce an additive effect that resulted in the lowest cue-induced craving scores. As previously discussed, such findings are consistent with previously studies reporting sensorimotor cues and nicotine administration to independently reduce craving while the combination of sensorimotor cues and nicotine delivery produced the greatest reductions (Rose et al., 2000).

It should be noted that while the QSU-Brief scores suggest nicotine lozenges alone may be more effective in attenuating cue-induced cravings than e-cigarettes with placebo lozenges, the VAS reports comparable levels despite participants not having received any nicotine from the e-cigarettes with placebo lozenges condition. Moreover, as previously mentioned, the VAS and QSU-Brief Factor 2 subscale scores reported using e-cigarettes with nicotine lozenges did not produced statistically
significant increases in craving after smoking cue presentation while both e-cigarettes with placebo lozenges and nicotine lozenges alone conditions produced significant increases. These findings are consistent with previous trials reporting nicotine delivery alone will reduce general cravings but have no significant impact on cue-induced cravings (Leischow et al., 1997; Rose, Herskovic, et al., 1985; Tiffany et al., 2000).

Moreover, the VAS, total QSU-Brief, and Factor 1 subscale found using e-cigarettes with nicotine lozenges and taking nicotine lozenges alone resulted in significantly lower cue-induced cravings, when assessed one hour after administering conditions, in comparison to smoking tobacco cigarettes. The QSU-Brief Factor 1 subscale represents the desire and intention to smoke with smoking perceived as rewarding (Cox et al., 2001). This may be a result of differences in sublingual and pulmonary nicotine delivery profiles and pharmacokinetics such that nicotine from cigarette smoke reaches peak plasma concentration within 20 minutes of smoking and rapidly decreases since nicotine is readily metabolized by CYP2A6 and has a half-life of two hours (C. Bullen et al., 2010; Le Houezec, 2003). Conversely, nicotine administered through the oral route has a more gradual increase in nicotine concentration, reaching peak plasma concentrations within two hours (Choi et al., 2003). As a result, the extended availability of nicotine from lozenges one hour after condition administration may have contributed to the significantly lower cue-induced craving during e-cigarettes with nicotine lozenges and nicotine lozenges alone conditions in comparison to the tobacco cigarette condition by continuing to produce positive reinforcing effects.

Conversely, the Factor 2 subscale found no significant differences in cue-induced craving between all conditions. Since the Factor 2 subscale represents the anticipation of relief from negative affect with an urgent desire to smoking (Cox et al., 2001), this finding suggests smoking cue presentations to induce similar levels of negative affect throughout all conditions.

4.2.3. Withdrawal-Induced Cravings

While differences in withdrawal-induced craving, assessed three hours after condition administration, among the four experimental conditions were not significant, the largest withdrawal-induced craving was observed during the tobacco cigarettes condition. As previously discussed, this may be a result of nicotine priming from briefly smoking tobacco cigarettes between long periods of smoking abstinence.

The QSU-Brief Factor 2 scores reported e-cigarettes with nicotine lozenges to significantly attenuate withdrawal-induced cravings. Similarly, while significant withdrawal-induced cravings were detected using the VAS, total QSU-Brief, and Factor 1 subscale, the lowest withdrawal-induced craving was observed during the e-cigarettes with nicotine lozenges condition. The findings of the current study are consistent with previously reports of cumulative craving reduction effects when sensorimotor cues and nicotine delivery are administered in combination (Rose et al., 2000).
Interestingly, the VAS and QSU-Brief Factor 1 observed comparable levels of withdrawal-induced cravings between the e-cigarettes with placebo lozenges and nicotine lozenges alone condition. Similar findings were reported in a study investigating the influence of sensory stimuli in suppressing craving and withdrawal symptoms (Buchhalter et al., 2005). 32 participants completed three 5-day conditions during which they smoked nicotine cigarettes, denicotinized cigarettes, or no cigarettes. Smoking denicotinized cigarettes and nicotine cigarettes were found equally effective in suppressing withdrawal-induced craving and some withdrawal symptoms.

Moreover, the VAS, total QSU-Brief, and Factor 2 subscale found using e-cigarettes with nicotine lozenges and taking nicotine lozenges alone resulted in significantly lower cue-induced cravings in comparison to smoking tobacco cigarettes. The Factor 2 subscale reflects smokers’ the anticipation of relief from negative affect (Cox et al., 2001), suggesting nicotine delivered through lozenges may more significantly attenuate withdrawal symptoms three hours after condition administration in comparison to nicotine delivered from smoking. These findings are reflective of differences in sublingual and pulmonary nicotine delivery profiles (Choi et al., 2003) such that nicotine delivered from cigarette smoking produce faster and higher peak plasma concentrations while lozenges release nicotine more slowly and maintain a more stable and prolonged plasma nicotine concentration.

Conversely, while the QSU-Brief Factor 1 subscale reported withdrawal-induced cravings were only significantly lower during the e-cigarettes with placebo lozenges condition in comparison to the tobacco cigarettes condition, similar differences in withdrawal-induced cravings were observed during the e-cigarettes with nicotine lozenges and nicotine lozenges alone conditions. However, significance was not detected due to a greater variation (standard deviations) in the data.

The QSU-Brief Factor 2 scale analysis revealed using e-cigarettes with nicotine lozenges resulted in no significant withdrawal-induced cravings while significant cravings were observed during the tobacco cigarettes, e-cigarettes with placebo lozenges, and nicotine lozenges alone conditions. While not significantly different from the other conditions, tobacco cigarettes were the least effective in attenuating withdrawal-induced craving, followed by using e-cigarettes with placebo lozenges, taking nicotine lozenge alone, and using e-cigarettes with nicotine lozenges. Moreover, in comparison to tobacco cigarettes, e-cigarettes with nicotine lozenges resulted in significantly lower withdrawal-induced cravings.

In summary, our study is one of few to conduct a dissociative investigation of the effects of nicotine delivery and behavioral cues on cigarettes craving. Moreover, this study is the first to do so using non-nicotinic e-cigarettes. In the current study, while smoking tobacco cigarettes was the most effective at reducing acute cigarette craving, using non-nicotinic e-cigarettes with nicotine lozenges most effectively attenuated cue and withdrawal-induced cravings. Findings suggest prolonged craving reduction observed during the e-cigarettes with nicotine lozenges condition may be a cumulative effect of concurrently using non-nicotinic e-cigarettes and receiving nicotine from lozenges. Moreover, using e-
cigarettes with placebo lozenges was also found to more effectively attenuate cue and withdrawal-induced cravings in comparison to tobacco cigarettes despite not delivering nicotine to participants. The results from the current study suggest e-cigarettes effective reduce cigarette craving regardless of nicotine content.

4.3. Mood Assessments

During the tobacco cigarette condition, while no significant differences were observed in positive affect PANAS and VAS scores when assessed post-neutral cues one hour after smoking, a significant reduction in negative affect scores were observed when measured one hour after smoking. Other cue-induction studies have found mood and cravings are correlated such that during periods of smoking abstinence and increased craving following presentation of smoking cues, positive affect decreases while negative affect increases (Bailey, Goedeker, & Tiffany, 2010; B. L. Carter & Tiffany, 2001; Warthen & Tiffany, 2009; Wray, Godleski, & Tiffany, 2011). Therefore decreases in positive affect and increases in negative affect are often described as a symptom of withdrawal (Hughes, 2007; Leventhal, Waters, Moolchan, Heishman, & Pickworth, 2010). These reports are consistent with those of the current study such that the reduction of negative affect reflects the significant decrease in cigarette craving reported one hour after smoking tobacco cigarettes. Conversely, the significant increases in negative affect scores reported post-smoking cues one hour after smoking and post-neutral cues and post-smoking cues three hours after smoking reflects the significant cue- and withdrawal-induced cravings observed during the tobacco cigarette visit.

Significant decreases in positive affect were reported following the presentation of smoking cues one hour after smoking, as well as following the presentation of neutral cues three hours after smoking tobacco cigarettes. These findings reflect the significant cue- and withdrawal-induced cravings experienced during the tobacco cigarette condition previously described. Similarly, the significant withdrawal-induced craving reported during the e-cigarettes with placebo lozenges condition is reflected in the significant decreases in positive affect were observed three hours after condition administration.

A significant increase in negative affect was observed three hours after using nicotine lozenges alone support previous observations that withdrawal-induced cravings were significant during the nicotine lozenges alone condition. No significant differences in negative affect scores were reported throughout the study visits during which participants used e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges.

No significant differences in both positive and negative affect, as measured by PANAS and VAS, were found during the e-cigarette with nicotine lozenges condition. These findings support previous observations that the use of e-cigarettes more effectively attenuated cue- and withdrawal-induced cravings.
Findings of the current study are consistent of those of previous cue-induction studies such that the increases in negative affect and decreases in positive affect reflect elevation of cue and withdrawal-induced cigarette cravings (Bailey et al., 2010; B. L. Carter & Tiffany, 2001; Warthen & Tiffany, 2009; Wray et al., 2011).

4.4. Gender Differences

As previously mentioned, smoking cessation trials have reported lower rates of successful smoking cessation with nicotine replacement therapy (NRT) in women compared to men (Bjornson et al., 1995; Gourlay et al., 1994; Swan et al., 1997). Moreover, NRT has been suggested to more greatly suppress withdrawal symptoms and reduce craving in males (Killen et al., 1990; Wetter et al., 1999) as men are more discriminatory towards nicotine doses (Perkins et al., 2002). However, the underlying mechanism contributing to differing rates of smoking cessation is unclear.

In the present study, no significant differences were observed in the demographics of male and female participants. Similarly, no significant differences in smoking topography and craving were found between genders during various smoking conditions.

More in-depth analysis of cravings by gender revealed findings similar to those regarding the whole sample. Smoking tobacco cigarettes was found to be the most effective at reduce acute cigarette cravings. However, the condition resulted in the greatest measured cue and withdrawal-induced cravings. Conversely, using e-cigarettes with nicotine lozenges produced the lowest cue and withdrawal induced cravings.

Similar to many previous studies investigating subjective craving and withdrawal symptoms suppression (Evans et al., 2006; Pomerleau et al., 2005), no significant differences in craving were observed at various time points between genders.

Interestingly, female participants reported no significant cue-induced cravings, as measured by the QSU-Brief Factor 1 subscale, during the e-cigarettes with nicotine lozenges and e-cigarettes with placebo lozenges conditions. These findings suggest female participants experience significant reinforcing effects from behavioral stimuli and are consistent with findings from previous trials. Several studies have reported women to be more sensitive to the non-nicotinic effects and stimuli of smoking (Perkins et al., 1999; Perkins et al., 1994). One study of denicotinized cigarettes observed women to report greater reductions in craving (Barrett, 2010). Conversely, no significant cue-induced cravings were reported during the nicotine lozenge alone condition in male participants. These findings suggest significant reinforcing effects in male participants to be driven by nicotine administration and are similar to results of previous studies reporting men to be more sensitive to the reinforcing effects of nicotine (Perkins et al., 2009; Perkins et al., 2002).
Though not significant, female participants often report higher levels of craving. However, female participants also consistently reported greater cigarette craving reductions than male participants throughout all the conditions and assessment time points (see Table 3.23). Since subjective cravings were measured through self-report, these observations may be a result of gender differences in sensitivity and awareness of physiological responses (Roberts, 1995). Moreover, the larger reduction in craving in female participants is similar to observations in a previous study reporting females to experience more negative mood symptoms after overnight smoking abstinence and greater withdrawal relieve after resuming cigarette smoking after a period of smoking abstinence (J. Xu et al., 2008).

4.5. **Physiological Changes**

During the nicotine lozenges alone and both e-cigarette conditions, significant decreases in CO were observed between the beginning and end of the study visits. This finding is congruent with previous studies that have reported acute e-cigarette exposure to not increase exhaled CO (Farsalinos et al., 2014; Vansickel et al., 2010).

Decreased heart rate was observed during all conditions at the end of visit in comparison to the start. Since decreases in heart rate is a symptom of nicotine withdrawal (Hughes, 2007; Leventhal et al., 2010), these results support previous observations of significant withdrawal induced cravings during various conditions. Moreover, while nicotine was delivered through smoking tobacco cigarettes and nicotine lozenges during various conditions, heart rate was assessed at the end of visit, three hours after the condition administration. Since heart rate has been associated with plasma nicotine concentrations (Evans et al., 2006) and the half-life of nicotine was approximately two hours, decreased measurements at the end of visit may reflect the depleted plasma nicotine concentration. Moreover, while participants are given time to rest upon arrival for study visits, their heart rate may be elevated as a result of physical activity. Conversely, participants remained in the clinic lounge for the entirety of the visit and were well rested when their heart rate was assessed at the end of study visits.

Similarly, no significant differences in systolic and diastolic blood pressure were observed during the e-cigarette with placebo lozenges condition since participants were not administered nicotine. Nicotine has been found to increase diastolic blood pressure (Soria et al., 1996). Conversely, decreases in blood pressure is often describe as a symptom of nicotine withdrawal (Hughes, 2007; Leventhal et al., 2010). No significant differences in systolic and diastolic blood pressure were observed during the tobacco cigarette visit. These findings are reflective of previous observations that cravings measured at the end of visit were similar to those measured at baseline when participants were overnight smoking abstinent and experiencing nicotine withdrawal. Significant increases in blood pressure were observed between the beginning and end of visits during which participants were administered nicotine lozenges alone and e-cigarettes with nicotine lozenges. This finding suggests plasma nicotine concentration may have still
been elevated at the end of visit, which may have contributed to the prolonged attenuation of cigarette craving during those conditions.

4.6. Limitations

While the current study is the first to evaluate craving reductions in regards to using non-nicotinic e-cigarettes in conjunction with nicotine replacement therapy, it contains various limitations. Participants recruited had never used e-cigarettes prior to the current study. As previously discussed, smoking behavior and subjective effects are associated with user experience. This was counterbalanced by the partial Latin-Square randomization design, whereby the differences in smoking topography seen between the first and second e-cigarette visits were no longer observed when the data were analyzed by e-cigarettes with placebo lozenges and e-cigarettes with nicotine lozenges conditions. That said, these results may not be applicable to experienced e-cigarette users. Moreover, participants underwent brief smoking conditions, lasting only 5 minutes. Longer e-cigarette or tobacco cigarette exposure may have more significantly reduced cravings and withdrawal symptoms. However, in the current study, participants were able to smoke at least one tobacco cigarette and take approximately 20 puffs on e-cigarettes during the allotted 5-minute smoking period.

The brand of nicotine lozenges used in the current study was also different between participants. While the first 39 participants used Nicorette® Mini lozenges, due to stock shortages, the remaining 4 participants were given Life Brand Mini lozenges. The dosage and contents of the both lozenges were identical and participants received lozenges from the same brand throughout their visits. Moreover, no significant differences in craving, assessed by the QSU-Brief, were observed between the two brands of lozenges. However, since only 4 participants used the Life Brand Mini lozenges, the statistical analysis was not sufficiently powered to detect significant differences.

Most importantly, the e-cigarettes used in the current study did not contain nicotine due to Health Canada regulations. Alternatively, it was decided during the development of the study protocol to administer nicotine using mini nicotine lozenges. This was a strength of the current study design as it allowed for the effects of behavioral cues and nicotine administration on cigarette craving to be dissociated. As a result, the findings from the current study are not indicative of the effectiveness of nicotinic e-cigarettes to reduce cigarette cravings and withdrawal symptoms. Instead, the results evaluated the effectiveness of placebo e-cigarettes as well as their concurrent use with proven nicotine cessation therapy to reduce cigarette cravings and withdrawal symptoms and potentially improve treatment outcomes.

Although participants indicated they had not tried e-cigarettes prior to the study, many noted during the initial phone screening they had friends or acquaintances that previously or currently use e-cigarettes. However, perceptions of e-cigarette use were not quantified at any time during the study. If participants
believed e-cigarettes to be effective in reducing cigarette craving and withdrawal symptoms, this may have influenced levels of craving reduction reported during the visits in which e-cigarettes were used.

Similarly, participants were not explicitly asked whether they thought the e-cigarettes and lozenges they received contained nicotine. A previous study reported smokers’ beliefs about the nicotine content of e-cigarettes significantly contribute to subjective craving and withdrawal symptoms (Copp, Collins, Dar, & Barrett, 2015). Therefore if participants believed the e-cigarettes and lozenges they received contained nicotine after condition administration, it may cause lower subjective craving scores to be reported during subsequent assessments that visit, and vice versa.

A further limitation of the study was the compliance of lozenge use. Although detailed instructions were provided to participants as to how to use the lozenges, including a demonstration on where to place the lozenges, no biochemical verification was conducted. The participants were observed placing the lozenges in their mouths; however, plasma nicotine and cotinine concentrations were not measured to determine the nicotine delivery profile from lozenges used in the current study.

Similarly, no control group was included to use placebo lozenges alone. This was a decision made during the development of the study design as an abundance of literature had already evaluated the effectiveness of nicotine and placebo lozenges to reduce cravings and withdrawal symptoms (Stead et al., 2008). However, the inclusion of a placebo lozenge alone condition may have acted as a double negative control condition, providing more insight into the influence behavioral cues and the effects of nicotine administration on craving reduction and withdrawal symptoms in the current study.

Moreover, the current study evaluated cigarette craving and withdrawal symptoms through only self-report. Despite the use of validated questionnaires, the study may have benefitted from the inclusion of objectives measures such as cognitive performance. Moreover, while vitals were measured at the beginning and end of each study visit, assessments were not done at various time points throughout the sessions. Craving reductions and withdrawal symptoms may have been correlated with changes in heart rate or blood pressure as a result of nicotine administration from lozenges. However, results from objective measures have been found similar to those from subjective measures (Wetter, Fiore, Baker, & Young, 1995).
5. **Conclusions**

The primary objective of this study was to evaluate the efficacy of e-cigarettes in alleviating craving by satiating behavioral cues associated with cigarette smoking. It was found that all conditions statistically significantly reduced acute cigarette cravings, measured post-neutral cues presented one hour after conditions. While smoking tobacco cigarettes most significantly reduced acute craving, the condition was least effective at attenuating cue- and withdrawal-induced cravings over time. Conversely, using e-cigarettes with nicotine lozenges resulted in the lowest reported cue- and withdrawal-induced cravings. Moreover, this study found using non-nicotine e-cigarettes to more effectively attenuate cue- and withdrawal-induced cravings in comparison to smoking tobacco cigarettes. Furthermore, the e-cigarette naïve participants enrolled in the current study were found to use e-cigarettes more intensively than tobacco cigarettes by taking significantly more and longer puffs with shorter interpuff intervals.
6. **Future Directions**

Although the present study suggests non-nicotine e-cigarettes may be effective in alleviating cigarette cravings, especially when used in tandem with nicotine lozenges, further study is required to better understand the influence of behavioral cues on cigarette craving. Past studies have reported similar findings using a combination of low nicotine yield cigarettes and transdermal nicotine patches; however, this study is the first to investigate subjective effects of using a combination of non-nicotinic e-cigarettes and NRT.

Due to regulatory restrictions, the current study used non-nicotinic e-cigarettes and administered nicotine through lozenges. The findings of the current study suggest differences in the nicotine delivery profiles of cigarette smoke and lozenges may affect reported cravings. As a result, findings cannot be generalized to effects of nicotinic e-cigarettes. Moreover, the current study did not investigate participant perception of the effectiveness of e-cigarettes as well as their expectancy of nicotine content in the conditions administered.

Similarly, first-generation disposable e-cigarettes that visually mimic tobacco cigarettes were used in this investigation. With the emergence of newer e-cigarette generations that have little or no resemblance to traditional tobacco cigarettes, further research is required to understand differences in sensory cue effects on craving when using devices that less closely resemble cigarettes. Given the customizability of new e-cigarettes, future studies may investigate device features and qualities e-cigarette users prioritize and prefer.

While concurrent use of non-nicotinic e-cigarettes with NRT may alleviate cigarette craving, further investigation is required to evaluate whether this condition may be an effective approach to long-term smoking cessation.

Furthermore, research studies to date have shown that e-cigarettes produce fewer and lower levels of toxic compounds in comparison to tobacco cigarette smoke. However, the long-term effects of daily e-cigarette use are unknown. Therefore, despite some findings suggesting e-cigarettes may be potential smoking cessation aids, the lack of data regarding chronic use precludes suggesting e-cigarettes to be used as safe harm reduction and smoking cessation aids.
References


APPENDIX 1

Informed Consent Package
E-CIGARETTES IN DAILY DEPENDENT SMOKERS
Study Information and Consent Form

Study Title:
A behavioral assessment of electronic cigarettes in reducing cue- and withdrawal-induced craving in daily dependent smokers

Investigators:
Principal Investigator: Laurie Zawertailo, PhD 416-535-8501 ext. 77422
Co-Investigator: Peter Selby, MBBS 416-535-8501 ext. 36859
Graduate Student: Ginnie Ng, BSc 416-535-8501 ext. 77298

Person to Contact About Research: Dr. L. Zawertailo 416-535-8501 ext. 77422

Purpose of the Study:
To evaluate differences in cigarette craving after smoking a conventional cigarette, an electronic cigarette (e-Cigarette) plus a nicotine lozenge or placebo lozenge, and taking a nicotine lozenge or placebo lozenge alone.

Procedures:
If you volunteer for the study, it will take 4 hours of your time (from 9 am to 1 pm) for 4 visits over 2 to 4 weeks. You must refrain from eating, drinking (except water), and smoking twelve hours before each study visit. You will be asked questions about your medical health, use of tobacco, and general well-being. Questions may involve information of a sensitive nature. If any of the questions make you feel uncomfortable, you do not have to answer.

Study Visits:
Your participation in this study will begin after signing the informed consent form on the last page of this package.

You will arrive in the lobby of 250 College St at 09:00AM on the day of your scheduled visit. A researcher will pick you up from there and a standardized breakfast will be provided. Your vitals (blood pressure, heart rate, and temperature) will then be taken and you will be asked to complete a set of baseline questionnaires. You will then be given 5 minutes to smoke either a tobacco cigarette, an electronic cigarette that may or may not contain nicotine, or use only a lozenge. The condition you receive at each visit will be randomized. During visits when you use an e-cigarette, you will not know which e-cigarette you are given because the devices will be identical; only the researchers will know. At the same time you will be given a lozenge to place between your cheek and gum. This lozenge may or may not contain nicotine; only the researchers will know. Similarly, when you are using only a lozenge in place of smoking, the lozenge may or may not contain nicotine; only the researcher will know.
You will be videotaped while you are smoking so the researchers can analyze your smoking patterns. One hour after smoking, you will be presented a two series of photographs and asked to complete a set of questionnaires after each series to evaluate your cigarette craving. Three hours after smoking, you will again be presented two series of photographs and asked to complete sets of questionnaires.

At each study visit, you will be provided with TTC tokens for transportation to and from the clinic, and receive $30 after completing the first visit, $50 after completing the second visit, $70 after completing the third visit, and $90 after you complete the final visit for a total compensation of $240.

**Risks and Benefits:**

Overnight abstinence from smoking before study visits may cause mild discomfort. The most common side effects associated with e-Cigarettes include nausea, headache, chest pain, cough, and exhaustion. The most common side effects of the nicotine lozenge include indigestion, headache, heartburn, and sore throat. You will be monitored very closely by study personnel for any changes in your health.

By participating in this study, you will be providing research information on craving and withdrawal effects of e-Cigarettes and will be compensated at the end of each visit for your time.

**Confidentiality:**

After obtaining your consent and enrolling you in the study, you will be assigned a participant ID number, used to code all the data that will be collected throughout the study. All information you provide is confidential to the extent permitted by law and will only be available to investigators. Any reports or publications based on this study will not identify you in any way.

As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law.

As part of the Research Services Quality Assurance Program, this study may be monitored and/or audited by a member of the Quality Assurance Team. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and extent permitted by law.

This trial has been registered on clinicaltrials.gov in order to assure the study is conducted according to the protocol and the findings are published within a reasonable time frame.

**Withdrawal and Voluntary Participation:**

You may withdraw from the study at any time. Your treatment, if any, at CAMH will not be affected. Study investigators may also terminate your participation in the study if they feel that you are not fulfilling the requirements of the study. Again, this will not affect your access to treatment at CAMH.

**Contacts:**

If you have any further questions or desire further information about this study, you may contact Dr. Laurie Zawertailo at 416-535-8501, extension 77422. If you have any questions about your rights as a study participant, you may contact Dr. Padraig Darby, chair of the Research Ethics Board, Centre for Addiction and Mental Health, at 416-535-8501, extension 6876.
I, _______________________________ have read (or had read to me) the consent form for the study named A behavioral assessment of electronic cigarettes in reducing cue- and withdrawal-induced craving in daily dependent smokers. I understand that my role is that of a subject in this study. I have been given an opportunity to ask questions about this study. My questions, if any, have been answered to my satisfaction, so that I now understand the procedures to be followed in the study, the risks to me from my participation, and my right to the confidential treatment of the information that is collected about me. I also understand that participation in this study is entirely voluntary and that I may refuse to participate or I may withdraw from the study at any time without any consequences for my continuing care.

- The researcher or a member of the researcher’s staff has discussed with me the risks of participation in this study
- I have read all the information in the Study Information Sheet, and I have had time to think about the information, and all of my questions have been answered to my satisfaction
- I voluntarily agree to participate in this research study, to follow study procedures, and to provide necessary information to the researcher as requested
- I am under no pressure to participate in the study, and I understand that I may withdraw from the study at any time. I understand that my participation in the study may be terminated by the study investigator/researcher if necessary
- By signing this consent form, I am not giving up my legal rights or releasing the investigators, researchers, or sponsors from their legal and professional obligations
- I have a copy of the Information Sheet and will receive a copy of this signed consent form

NAME OF PARTICIPANT ___________________________ SIGNATURE OF PARTICIPANT ___________________________ DATE _______________________

NAME OF INDIVIDUAL OBTAINING CONSENT ___________________________ SIGNATURE OF INDIVIDUAL OBTAINING CONSENT ___________________________ DATE _______________________

NAME OF INVESTIGATOR ___________________________ SIGNATURE OF INVESTIGATOR ___________________________ DATE _______________________

Subject Initials : ___________
APPENDIX 2

Study Advertisements
Are you curious about the electronic cigarette?

The Nicotine Dependence Clinic at the Centre for Addiction and Mental Health (CAMH) invites individuals who smoke regularly and are interested in trying electronic cigarettes to participate in a study.

To be eligible, participants must:

Have no intention to quit smoking in the next 3 months

Be able to attend 4 scheduled 4-hour sessions (from 9AM to 1PM) on a weekday

Be aged 18 to 65

Be mentally and physically healthy

Not be pregnant, trying to conceive, or breastfeeding

Confidential Inquiries: (416) 535-8501 ext. 77298
Electronic cigarettes provided free of charge; Compensation provided

To find out about other treatments and services for mental illness or addiction, please call CAMH at (416) 535-8501
APPENDIX 3

Phone Eligibility Screening and Scheduled Visit Email Reminder
E-Cigarettes in Daily Dependent Smokers

Phone Screening Script

Date: ____________________________  Phone (H): ____________________________

Name: ____________________________  (C): ____________________________

Email: ____________________________  (W): ____________________________

Hello, may I please speak to [subject]?

- If not there: Thank you, I’ll call again later
- No information about CAMH should be given since it may jeopardize the subject’s confidentiality

Reasons for Exclusion:

Hi, this is Ginnie. I am calling from the Centre for Addiction and Mental Health. I understand that you are interested in an electronic cigarette research study and was hoping to give you more information as well as get some information from you. This will take about 10 minutes, is this a good time for you?

- If not: When is a good time to call you? ___________

This study is designed to investigate the effectiveness of electronic cigarettes in reducing smoking craving and withdrawal symptoms. Electronic cigarettes are new nicotine delivery devices often designed to mimic tobacco cigarettes in feel and taste. Instead of burning tobacco, electronic cigarettes produce vapor from a battery-powered heating element and cartridges.

The study involves attending 4 sessions over several days. Each session will take approximately 4 hours, from 9AM to 1PM. You will be asked to abstain from food, drinks (with the exception of water), and smoking the night prior to arriving. At each visit, you will first be provided a standard breakfast, have basic vital signs taken (weight, blood pressure, heart rate) and asked for a breath sample to confirm overnight abstinence from smoking. Then you will be given a tobacco cigarette, an electronic cigarette with nicotine, an electronic cigarette without nicotine, or a Nicorette® lozenge to use. This part of the study will be videotaped so researchers can analyze your smoking patterns. You will then be shown a series of images and asked to complete some questionnaires.

After each session, you will be provided TTC tokens for transportation to and from the clinic. You will also receive monetary compensation after the completion of each study session. The value will increase with each completed visit.

All private information that could be used to identify you will remain confidential and you will not be identifiable.

Do you have questions? Are you interested in participating?

Great! During this phone screening, we need to determine if you qualify for participation in this study. I just have a few standard questions to ask, so please answer each as best as you can.
E-Cigarette Craving Phone Screening Script · May 2014

1. Is it OK to leave messages at this phone number? __________________________________________

2. Where did you hear about this study? ____________________________________________________

3. Gender:  ○ Male  ○ Female

4. How old are you? ______________________  DOB: __________________________________________
   * If < 18 or > 65, exclude

5. Have you been a research participant before?  ○ Yes  ○ No

6. Have you used an e-cigarette before?  ○ Yes  ○ No  If yes, exclude

7. What is your highest level of education? __________________________________________________
   * If < grade 7, exclude

8. Do you aim to stop smoking and set a quit date?  ○ Yes  ○ No  If yes, exclude

9. Females only:
   a. Are you currently pregnant?  ○ Yes  ○ No  If yes, exclude
   b. Are you currently trying to conceive?  ○ Yes  ○ No  If yes, exclude
   c. Are you currently breastfeeding?  ○ Yes  ○ No  If yes, exclude

10. How soon after you wake up do you smoke your first cigarette?
    3 – ○ Within 5 minutes  1 – ○ 31 to 60 minutes
    2 – ○ 6 to 30 minutes  0 – ○ After 60 minutes

11. Do you find it difficult to refrain from smoking in places where it is forbidden?
    1 – ○ Yes  0 – ○ No

12. Which cigarette would you hate most to give up?
    1 – ○ The first one in the morning  0 – ○ All others

13. How many cigarettes do you smoke per day? CPD: _________________________________________
    3 – ○ 31 or more  1 – ○ 11 to 20
    2 – ○ 21 to 30  0 – ○ 10 or fewer  If < 10 per day, exclude

14. Do you smoke more frequently during the first hours after waking than during the rest of the day?
    1 – ○ Yes  0 – ○ No

15. Do you smoke if you are so ill that you are in bed most of the day?
    1 – ○ Yes  0 – ○ No

   FAGERSTROM SCORE: __________________________________________  If < 3, exclude

16. Are you able to attend sessions from 9AM to 1PM on at least one day of the working week (i.e. Monday to Friday)?  ○ Yes  ○ No  Which days? ____________________
I don’t have any more questions for you. Do you have any questions?

Are you still interested in participating?
- If no: Thank you for your time
- If yes: When are you available to come in for the first session? ______________________________
  o We will be providing breakfast at the beginning of each session. Do you have any dietary restrictions? ______________________________

THINGS TO REMEMBER BEFORE COMING IN:

- Sessions take up to 4 hours and we need you to refrain from eating, drinking (except for water), and smoking 12 hours before arriving in the morning
- If you wear reading glasses or contact lenses, please have them with you when you come in
- Please wear a short sleeve shirt to facilitate heart rate and blood pressure measurements
- This study takes place at 33 Russell Street, at the corner of College and Spadina
- If you are unable to keep your appointment, please call in advance so we can promptly reschedule you. My phone number is 416-535-8501 extension 77298
- Can I send you these reminders by email? ○ Yes ○ No

Your session is scheduled for ______________________________, so please make sure you refrain from smoking, eating, and drinking starting at 9PM the night before, no later.

Thank you for your time.

Interviewer: _______________________________ Signature: _______________________________
Hi [NAME],

As discussed on the phone, here are some things to remember before coming in for your study visit:

- **Do not eat, drink** (except for water), and **smoke 12 hours before arriving** in the morning.
- If you wear reading glasses or contact lenses, please have them with you when you come in.
- Please wear a short sleeve shirt to facilitate heart rate and blood pressure measurements.
- This study takes place at CAMH located in downtown Toronto at **250 College Street** at the corner of College and Spadina. Enter from the main doors on College Street and wait in the lobby, a researcher will arrive shortly to take you to the clinic.
- If you are unable to make your appointment, please call in advance (416-535-8501 extension 77298) so we can promptly reschedule your session.

- **PLEASE BRING A PACK OF YOUR USUAL TOBACCO CIGARETTES TO YOUR FIRST STUDY VISIT**

250 College St, Toronto ON, M5T 1R8
(416) 535-8501 ext 77298

Transit: Take the 510 Spadina streetcar and exit at College Street, or take the 506 College streetcar and exit at Spadina Avenue. You will receive 2 TTC tokens at each visit.

Parking: Underground parking is on a first come first serve basis. Entrance is off Spadina, north of College. You are required to pay for your own parking.

Your session is scheduled for:

**[DAY OF WEEK], [DATE] AT 9:00 AM**

Please make sure you refrain from smoking, eating, and drinking starting at 9PM the night before.

THANK YOU!
APPENDIX 4

Example of Cue Slideshow Images
Neutral Cues Presentation Images
Smoking Cues Presentation Images
APPENDIX 5

Questionnaires
1. Date of Birth: _______/_______/_______

2. Current Age: _______________________

3. Gender:  ○ Female  ○ Male

4. What is your current employment status?
   ○ Full Time
   ○ Part Time
   ○ Self-Employed
   ○ Unemployed
   ○ Retired
   ○ Unknown

5. Are you currently a student?  ○ Yes  ○ No

6. Are you currently receiving disability benefits from your employer or government?
   ○ Yes  ○ No

7. What is the highest level of education you have completed?
   ○ Less than High School
   ○ High School Diploma
   ○ Some College
   ○ College Diploma
   ○ Some University
   ○ University Degree
   ○ Post-Graduate
   ○ Unknown

8. What is your approximate gross household income in 2013 (i.e. income from all sources before income tax reduction)?
   ○ Less than $10,000
   ○ $10,001 to $20,000
   ○ $20,001 to $40,000
   ○ $40,001 to $60,000
   ○ $60,001 to $80,000
   ○ $80,001 to $100,000
   ○ Over $100,000
   ○ No Income
   ○ Unknown

9. What is your ethnic background?
   ○ European / Caucasian
   ○ African Descent / African American
   ○ East Indian
   ○ Asian (Chinese, Japanese)
   ○ Hispanic / Latino
   ○ Native North American
   ○ Pacific Islander
   ○ Other: ___________________________

10. At what age did you smoke your first whole cigarette? _____________________________________

11. At what age did you begin to smoke cigarettes occasionally? _____________________________

12. At what age did you begin to smoke cigarettes daily? _________________________________

13. Do you use other tobacco products?
   ○ Yes  ○ No
   If ‘YES’, what other tobacco products are you currently using?
   ○ Cigars
   ○ Tobacco Water-Pipe (Hookah)
   ○ Pipe Tobacco
   ○ Pinch or Snuff
   ○ Others: ___________________________

14. Do you use other nicotine products?
   ○ Yes  ○ No
   If ‘YES’, what other tobacco products are you currently using?
   ○ Transdermal Patches
   ○ Inhalers
   ○ Gum
   ○ Lozenge
   ○ Others: ___________________________

Subj. Initials: _______________ Subj. No: _______________
### Fagerstrom Test for Nicotine Dependence

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
</table>
| 1. How soon after you wake up do you smoke your first cigarette?        | - Within 5 minutes
                                                                 | - 6 to 30 minutes
                                                                 | - 31 to 60 minutes
                                                                 | - After 60 minutes                          |
| 2. Do you find it difficult to refrain from smoking in places where it is forbidden? | - Yes
                                                                 | - No                                        |
| 3. Which cigarette would you hate most to give up?                      | - The first one in the morning
                                                                 | - All others                                 |
| 4. How many cigarettes do you smoke per day?                           | - 31 or more
                                                                 | - 21 to 30
                                                                 | - 11 to 20
                                                                 | - 10 or fewer                                |
| 5. Do you smoke more frequently during the first hours after waking than during the rest of the day? | - Yes
                                                                 | - No                                        |
| 6. Do you smoke if you are so ill that you are in bed most of the day?   | - Yes
                                                                 | - No                                        |

**FAGERSTROM SCORE**: ____________________

Subj. Initials : _____________ Subj. No : _____________
### E-CIGARETTES IN DAILY DEPENDENT SMOKERS STUDY
#### QSU – BRIEF

Please answer each of the following questions by circling the number that most closely represents how you are feeling **right now**, using the 7-point scale.

1. **I have a desire for a cigarette right now.**

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

2. **Nothing would be better than smoking a cigarette right now.**

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

3. **If it were possible, I probably would smoke right now.**

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

5. **All I want right now is a cigarette.**

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
6. I have an urge for a cigarette.

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

7. A cigarette would taste great right now.

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

8. I would do almost anything for a cigarette right now.

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

9. Smoking would make me less depressed.

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

10. I am going to smoke as soon as possible.

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Somewhat disagree</th>
<th>Neutral</th>
<th>Somewhat Agree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
Example of QSU-Brief on Laptops

I have a desire for a cigarette right now.

- Strongly Disagree
- Disagree
- Somewhat Disagree
- Neutral
- Somewhat Agree
- Agree
- Strongly Agree

Next
E-CIGARETTES IN DAILY DEPENDENT SMOKERS STUDY
PANAS

This scale consists of a number of words that describe different feelings and emotions. Please read each item and then check the answer from the scale indicating to what extent you have felt this way over the past week.

<table>
<thead>
<tr>
<th></th>
<th>Very slightly or not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
</tr>
<tr>
<td>1. Interested</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. Distressed</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3. Excited</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4. Upset</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5. Strong</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6. Guilty</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7. Scared</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>8. Hostile</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9. Enthusiastic</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>10. Proud</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>11. Irritable</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>12. Alert</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>13. Ashamed</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>14. Inspired</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>15. Nervous</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>16. Determined</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>17. Attentive</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>18. Jittery</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>19. Active</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>20. Afraid</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

PA: ________________  NA: ________________
Example of PANAS on Laptops
This visual analogue scale (VAS) consists of a number of words that describe different feelings and emotions. Please indicate on the bar the number between 1 and 100 that best describes the intensity of each item you feel at the moment.

1. Calm (P)

2. Restless (N)

3. Alert (P)

4. Irritable (N)

5. Drowsy (N)

6. Confused (N)

7. Energetic (P)

8. Sharp (P)
9. Apathetic (N)

10. Strong (P)

11. Unfulfilled (N)

12. Depressed Mood (N)

13. Weak (N)

14. Satisfied (P)

15. Stressed (N)

16. Relaxed (P)

17. Nervous (N)

18. Angry (N)

19. Scattered (N)
20. Happy (P)

21. Attentive (P)

22. Anxious (N)

23. Focused (P)

24. Frustrated (N)

25. I have a desire for cigarettes right now

26. If possible, I would smoke a cigarette right now

27. All I want right now is a cigarette

28. I have an urge for cigarettes

29. I crave cigarettes right now

(P) denotes positive effects
(N) denotes negative effects
Example of VAS on Laptops
Please check the symptoms below that you have experienced during the study visit.

- Anxiety
- Fatigue
- Dry Throat
- Confusion
- Hallucinations
- General Weakness
- Sore Tongue
- Chest Pain
- Excessive Sweating
- Vomiting
- Numbness or Tightness
- Difficulty Breathing
- Gas or Bloating
- Nausea
- Trouble Swallowing
- Wheezing
- Diarrhea
- Memory Loss
- Palpitations (Heart Pounding)
- Muscle Weakness
- Skin Rash
- Joint Stiffness
- Blurred Vision
- Loss of feeling in any body part
- Increased Salivation
- Drowsiness
- Joint Pain
- Abdominal Pain
- Unusually Hot
- Sore Throat
- Clumsiness
- Nasal Congestion (Stuff Nose)
- Tremor (Shakes)
- Headaches
- Dry Mouth
- Back Pain
- Dizziness or Fainting
- Difficulty Walking
- Loss of Balance
- Agitation or Excitement
- Shortness of Breath
- Chills
- Loss of Appetite
- Heartburn
- Muscle Pain
- Facial Warmth
- Choking Sensation
- Inability to Concentrate
- Lightheadedness

Other Symptoms:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
APPENDIX 6

Examples of Electronic Cigarettes
SmokeNV Canadian Premium non-nicotinic disposable e-cigarettes used in the current study. Each pack contained two e-cigarettes and was marked with the corresponding participant number and initials.