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Parsing the Influences of Nicotine and Expectancies on the Acute Effects of E-Cigarettes: A Balanced-Placebo Experiment

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Parsing the Influences of Nicotine and Expectancies on the Acute Effects of E-Cigarettes: A
Balanced-Placebo Experiment

by

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A thesis submitted in partial fulfilment
of the requirements for the degree of
Master of Arts
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ABSTRACT

E-cigarette use has been increasing in recent years, and its ultimate public health impact is still unknown. In order to assess the addictive liability of these products, research is needed to investigate the roles of nicotine and other factors on psychological and physical effects of “vaping.” The goal of the current study was to investigate the role of expectancies, nicotine delivery, and their interactions on the effects of e-cigarette use via a balanced-placebo experiment. In this design, drug dosage (contains nicotine or not) was crossed with instructions (told nicotine or non-nicotine) during ad-lib e-cigarette use sessions by 128 current e-cigarette users. This design allows for parsing of the causal role of expectancies and pharmacology, as well as their interaction. Dependent variables included both psychological outcomes (cravings for cigarettes and e-cigarettes, mood, satisfaction, reward) and physiological variables (hunger, attention, aversion, respiratory tract sensations). Among cigarette smokers ($n=52$), a significant main effect of instruction emerged on reductions in craving to smoke, although moderation analyses revealed that this effect was limited to males. Overall, significant drug X instruction interactions were found on craving to vape, psychological reward, and enjoyment of respiratory tract sensations, indicating synergistic causal influences of both expectancies and nicotine. Expectancies, smoking status, and gender moderated some of these effects. The results of this study identified effects of e-cigarettes that were driven by either nicotine, cognitive drug expectancies, or both. Results should be considered in the context of methodological and theoretical limitations. This study contributes to the understanding of motivational influences

that may affect the initiation and maintenance of e-cigarette use, which may guide the development of public health and clinical interventions.

INTRODUCTION

Tobacco use is one of the leading causes of death and disability in the United States (USDHHS, 2014); however, population-based interventions, public policies, and media campaigns have successfully prompted a decrease in smoking rates (CDC, 2012; Jamal et al., 2014). More recently, there has been a shift in the landscape of tobacco use with the introduction of novel products such as electronic cigarettes (e-cigarettes; Pepper & Eissenberg, 2014). E-cigarettes (or electronic nicotine delivery devices; ENDS) are becoming increasingly popular among both smokers and non-smokers (Caponnetto, Campagna, Papale, Russo, & Polosa, 2012). In fact, the most recent National Youth Tobacco Survey showed that despite significant decreases in cigarette smoking among adolescents, overall tobacco use rates remain largely unchanged from 2013 to 2014 due to the increase of use in e-cigarettes (USDHHS, 2015). E-cigarette use more than doubled from 2010 (1.8 - 3.3% ever use, 0.3 - 1.0% current use) to 2013 (8.5 - 13% ever use, 2.6 - 6.8% current use) among all adults (King, Patel, Nguyen, & Dube, 2014; McMillen, Gottlieb, Shaefer, Winickoff, & Klein, 2014) and rates continue to increase, especially among current and former smokers (Fagerström, Etter, & Unger, 2015).

Since the introduction of e-cigarettes and their growing popularity, there have been conflicting viewpoints regarding the impact of these products on the population of smokers and non-smokers alike. Whereas some suggest potential harm-reduction benefits, especially among those unable or unwilling to quit smoking using conventional methods, others believe that these products present regulatory challenges and may increase nicotine dependence in those otherwise

not susceptible (Fagerström et al., 2015). Such polarized views have increased the need for both research and objective public policy in the area of e-cigarettes (Etter, Bullen, Flouris, Laugesen, & Eissenberg, 2011). This research agenda is especially important if e-cigarettes are to be used for clinical and therapeutic purposes in future trials and public health initiatives (Caponnetto et al., 2012).

E-Cigarettes

E-cigarettes are portable devices containing a battery attached to a heating element that aerosolizes liquid containing nicotine along with other constituents, typically propylene glycol and vegetable glycerin (Brown & Cheng, 2014; Ebbert, Agunwamba, & Rutten, 2015). Some devices are disposable, whereas others are rechargeable, refillable, and/or customizable. Disposable models (aka “first generation”) tend to look like cigarettes in size and shape, whereas second and third generation models are typically larger, and due to customization features, may not resemble a cigarette at all. As the latter devices are refillable and rechargeable, they can be customized to nicotine content, flavor, and aesthetic style. Nicotine content in the liquid solution typically peaks around 18-26mg/ml, but can go higher, and is also available as 0 nicotine content. Flavors include conventional tobacco and menthol flavors, but they are also available in an ever-increasing range of fruit, sweet, and savory flavor styles. Using e-cigarettes is often referred to as “vaping,” and users may self-identify as “vapers.”

Although they share some common characteristics, e-cigarettes have been shown to be less effective than traditional cigarettes at nicotine delivery, especially among novice users (Norton, June, & O'Connor, 2014; Trtchounian, Williams, & Talbot, 2010). Studies have found that e-cigarettes are inhaled differently than combustible cigarettes (Trtchounian et al., 2010). This may be due to the “learning curve” that is associated with vaping; previous research has shown that

nicotine intake differs with levels of experience and devices used, in that more experienced users consume more nicotine and self-report greater effects of nicotine than novice users (Vansickel & Eissenberg, 2013). Other studies have shown that transitioning from first to second generation devices is often prompted by the desire for more efficient nicotine delivery (Yingst et al., 2015). In fact, the device itself may have more of an impact on nicotine delivery than the level of nicotine in the cartridge or solution (Goniewicz, Hajek, & McRobbie, 2014)

Despite the inferior pharmacologic delivery properties of e-cigarettes, vaping is often reported to elicit fewer acute and aversive symptoms than smoking. Specifically, there is evidence that the effects of e-cigarettes on cardiac functioning, lung functioning, and inflammation are significantly less extreme than effects of cigarettes (Callahan-Lyon, 2014). In a review of surveys and studies utilizing ad-libitum sessions, it was found that vaping generally decreased cravings for cigarettes and produced other psychological outcomes associated with smoking (Evans & Hoffman, 2014). Results from these reviews suggest that vapers are replicating some aspects of the smoking experience despite inconsistencies in nicotine content and topography.

Reasons for E-cigarette Use

Because of high variability in available e-cigarette designs, nicotine contents, and flavors, there may be several reasons for an individual to use e-cigarettes. In one survey of over 1,300 e-cigarette users (with just 4 never-smokers), a majority of participants reported their reason for initiating use was as an alternative to traditional cigarettes (Dawkins, Turner, Roberts, & Soar, 2013). Other reasons include reduced health risk, cost, avoiding smoking restrictions, and quitting smoking. In fact, many e-cigarette users report quitting smoking or significantly reducing tobacco use after vaping initiation, independent of original intentions (Dawkins et al.,

2013; Siegel, Tanwar, & Wood, 2011). Preliminary follow-up findings indicate that dual product cessation is also observed in this population (e.g., Polosa, Caponnetto, Maglia, Morjaria, & Russo, 2014; Siegel et al., 2011). Some survey data also suggest that increased e-cigarette experimentation may not prompt significant use of other tobacco products (Meier, Tackett, Miller, Grant, & Wagener, 2015).

Studies directly examining the therapeutic potential of e-cigarettes for smoking cessation are limited due to regulatory issues and limited safety data. To date, only two randomized controlled trials with e-cigarettes have been conducted with smoking cessation as an outcome (Hartmann & Boyce et al., 2016). One study (Bullen et al., 2013) randomly assigned nicotine patches, nicotine e-cigarettes, and placebo (non-nicotine) e-cigarettes to participants interested in quitting smoking. Those receiving an e-cigarette were blind to the nicotine content. Results showed higher rates of cigarette abstinence at follow-up for those assigned to nicotine e-cigarettes as compared to the other groups, however, the differences were not statistically significant. These results suggest that using a nicotine e-cigarette may be just as effective as a nicotine patch in generating a successful quit attempt, and that nicotine content in the e-cigarette may not be critical. Another trial (Caponnetto et al., 2013) offered participants without intentions to quit the opportunity to try an e-cigarette and potentially reduce tobacco use. Participants were randomized to receive one of two nicotine doses or no nicotine and were blind to the content of their e-cigarette. A reduction in cigarettes smoked was observed across all groups, regardless of nicotine content. Results from both trials suggest that the novelty of e-cigarette use, along with the handling and manipulation qualities of e-cigarettes, may play an important role beyond nicotine in smoking cessation efforts. Overall, findings from the few randomized controlled trials (RCTs) and other cohort studies are somewhat mixed, but provide insight into the potential of

these products to be used as cessation devices (McRobbie, Bullen, Hartmann-Boyce, & Hajek, 2014).

Nicotine

A major focus in smoking research is examining the role of tobacco's primary psychoactive ingredient, nicotine. Nicotine is thought to be both a primary reinforcer of smoking and a reinforcement enhancer of other smoking-related stimuli (Caggiula et al., 2009). The self-administration of nicotine through cigarettes produces pharmacologic effects, including physiological and psychological effects, and affects non-pharmacologic aspects of smoking (e.g. taste and smell; Robinson & Pritchard, 1992). All of the aforementioned factors may contribute to the initiation and maintenance of smoking behaviors, as well as difficulties in cessation.

Nicotine replacement therapy (NRT; which is available in many forms such as transdermal patch and gum) provides nicotine without the use of a tobacco product, and has become a standard for tobacco cessation treatment (Fiore et al., 2000). However, some research has indicated that tactile factors associated with the act of smoking influence subjective reward to a greater degree than nicotine dose on its own (Rose, Behm, Westman, & Johnson, 2000). These data provide evidence of a relationship between the physiological, psychological, and non-pharmacologic addictive properties of nicotine from cigarettes. Because of this, it has been suggested that nicotine replacement alone may have upper limits as a cessation treatment, and future therapies should also address the habitual, sensorimotor cues associated with smoking (Rose, 2006).

Whereas conventional nicotine replacement products, such as patches and gum, were specifically developed and marketed for smoking cessation, e-cigarettes may provide similar nicotine delivery with more indirect cessation claims (Elam, 2015). As previously mentioned, e-

cigarette users often report vaping for cessation, or as an alternative, to combustible cigarettes. Recent studies have attempted to assess the role of nicotine in e-cigarette use, especially in terms of smoking cessation, but the results have been inconsistent as this research is in its infancy (Bullen et al., 2013; Caponnetto et al., 2013). Some research suggests that because the drug effects of nicotine are deeply reinforcing, nicotine in e-cigarettes may only exacerbate dependence on combustible products (Fillon, 2015; Kandel & Kandel, 2014). However, these claims are observational and theoretical in nature, and have not been empirically tested.

E-cigarettes not only facilitate nicotine delivery in a pharmacological sense, but they provide a habitual delivery mechanism that mimics smoking. Case studies of individuals who have quit cigarettes using e-cigarettes report the ritualistic reinforcing effects of nicotine delivery via e-cigarettes to be an important component of the cessation process (Caponnetto, Polosa, Russo, Leotta, & Campagna, 2011). In addition, nicotine from e-cigarette use has been shown to enhance sensory rewards and some other reinforcers with a similar, but less robust, effect as cigarettes (Perkins, Karelitz, & Michael, 2015). Consequently, some studies show that e-cigarette users show levels of dependence similar to that of NRT, but not as high as combustible cigarettes (Etter & Eissenberg, 2015; Foulds et al., 2014), although research in this area is preliminary.

Expectancy Theory

Another construct that may influence drug use and addictive behaviors beyond pharmacological properties are expectancies, which are learned, cognitive intervening variables. Historically, expectancy theories have been shaped by the dominating school of thought at the time, from behaviorists such as Tolman (1932), to cognitive and social learning theorists like Bandura (1977). Contemporary theory conceptualizes expectancies in a more expansive sense, as fundamental information processes that affect all behavior (Goldman, 1999). That is,

expectancies are essentially programmed into an individual through conscious mechanisms as well as modalities that are outside of one's consciousness. Therefore, in the case of drug use, expectancies amalgamate individual influences, including genetics, neurological networks, direct and vicarious experiences, and personality, along with social and cultural norms (Brandon, Herzog, Irvin, & Gwaltney, 2004; Goldman, Del Boca, & Darkes, 1999)

Drug-related expectancies are often characterized within the constructs developed by social learning theories (Bandura, 1977) that suggest individuals hold both "self-efficacy expectancies" and "outcome expectancies" about their behavior and its consequences (Brandon, Juliano, & Copeland, 1999). Self-efficacy expectancies incorporate thoughts regarding the ability to execute a behavior, such as quitting smoking or maintaining cessation. Outcome expectancies reflect the estimated responses and consequences elicited by a behavior; in this case, drug use. Outcome expectancies have received more attention in substance use research, particularly alcohol use, with respect to the roles of expectancies upon the initiation, maintenance, and cessation of use (Goldman, Brown, & Christiansen, 1987). Goldman et al. encourages research to explore the relationship between learned, cognitive, mechanisms, such as expectancies, and pharmacologic variables.

Several studies have attempted to elucidate the role of expectancies on smoking behavior. Previous research has shown that daily smokers hold higher positive outcome expectancies for smoking and do not endorse as many negative expectancies about immediate and long-term effects of smoking, compared to light smokers and non-smokers (Brandon et al., 1999). These positive expectancies can be predictive of future smoking in adolescents even when assessed before actual experimentation with cigarettes (Chassin, Presson, Sherman, & Edwards, 1991). However, smokers may attribute specific expectancies to smoking itself, and not nicotine. For

example, Hendricks and Brandon (2008) found that smokers attributed some similar outcomes to both smoking and nicotine, but were more likely to associate smoking with negative consequences and nicotine with addictive consequences. In the case of NRT, smokers are much less likely to attribute positive expectancies to NRT than cigarettes, which has implications for NRT treatment efficacy (Juliano & Brandon, 2004). Overall, results from these previous studies indicate that there may be expectancies attached to the specific act of smoking cigarettes that differ from the expectancies for the active ingredient, nicotine.

Expectancies and Drug Interactions

Prior studies have indicated that expectancies can potentially impact immediate drug use behaviors and outcomes to a greater degree than drug dosage itself (Kirsch, 1985); this is often referred to as “the placebo effect.” In the field of alcohol, this phenomenon has been explored through simultaneous expectancy and pharmacological manipulation using the balanced placebo design (Hull & Bond, 1986). This paradigm utilizes a 2x2 factorial design in which drug type (active or placebo) is crossed with instructional set (told active or placebo). From this, the effects of both the pharmacologic properties of the drug and expectancies about the drug can be independently evaluated as causal influences upon various immediate drug use outcomes. Results from these studies using alcohol have indicated that the drug itself (alcohol) has predictable effects on non-social functions, such as cognitive domains, physical sensations, and motor skills; whereas expectancies about alcohol appear to affect socially influenced behaviors, such as increased alcohol consumption, sexual arousal, and aggression (Hull & Bond, 1986).

The pathway by which the balanced-placebo design reveals underlying expectancies as been described by distinguishing between “stimulus expectancies” and “response expectancies” (Perkins, Sayette, Conklin, & Caggiula, 2003). Stimulus expectancies are the individual’s beliefs

about the drug content, whereas response expectancies are the individual's beliefs about the drug effects (outcome expectancies, in Bandura's term). Stimulus expectancies are assumed to be driven, in the laboratory context, from the instructional set provided to participants. These, in turn, activate previously-developed response expectancies, which then generate the outcome effects.

Historically, there have been challenges implementing the balanced-placebo design with alcohol, as it can be difficult to carry out the alcohol dose manipulation without breaking the blind. That is, unless very low alcohol doses are used, participants can often detect the alcohol, regardless of instructional set. Such problems have led to criticisms of the paradigm (Martin & Sayette, 1993). The balanced placebo design has also been utilized in the smoking field to investigate the effects of expectancies and nicotine on several outcomes, such as mood, cognition, and physiological symptoms (Harrell & Juliano, 2012; Juliano & Brandon, 2002; Kelemen & Kaighobadi, 2007; Perkins et al., 2008; Perkins et al., 2009; Perkins et al., 2003). Similar to previous alcohol research, results from these studies demonstrate that the drug (nicotine) appears to have an effect on physiological domains, such as cognition and aversive physical symptoms, whereas expectancies may affect more emotionally salient domains, such as mood enhancement, satisfaction, and craving. Further research parsing drug effects and expectancies in drug use behaviors using balanced-placebo designs is encouraged (Brandon et al., 1999; George, Gilmore, & Stappenbeck, 2012).

Research on expectancies, drug interactions, and their effects on e-cigarette use is limited at present, and can be complicated because of variations in product type and user characteristics. One online survey of vapers (Harrell et al., 2014) found that e-cigarettes were preferred to traditional cigarettes in holding fewer health and addictive risks, as well as tasting better and

being more satisfying. Additionally, e-cigarettes were thought to be superior to NRT in reducing cravings with fewer aversive side effects. Similar findings have been seen in samples of hospitalized patients (Hendricks et al., 2014) and in focus groups (Barbeau, Burda, & Siegel, 2013). Furthermore, expectancies held may vary depending on concurrent cigarette smoking as well as intentions to discontinue e-cigarette use. “Dual users,” or individuals who use both traditional cigarettes and e-cigarettes, report fewer positive outcome expectancies than former smokers; whereas higher negative outcome expectancies are reported by those with intentions to quit e-cigarettes (Harrell et al., 2015). Additionally, there is some evidence that expectancies about e-cigarettes differ between genders. One study suggests that expectancies for craving reduction vary by gender, in that females might be more influenced by their pre-existing expectations (Copp, Collins, Dar, & Barrett, 2015). Other research suggests that females use e-cigarettes for mood-management and weight control more than males, who use e-cigarettes for smoking cessation more frequently than females (Piñeiro et al., 2016). Although the aforementioned evidence does provide insight, a majority of research involving e-cigarettes and expectancies is survey-based or observational research studies, and therefore, causality cannot be determined. Through the use of a balanced-placebo design, causality from two factors (drug and expectancies) can be tested.

The Present Study

The goal of the proposed study was to investigate mechanisms contributing to the addictive liability of e-cigarettes by examining the independent and combined effects of nicotine pharmacology and outcome expectancies. Essentially, the study was designed to elucidate causality by manipulating expectancies and drug dose in a balanced placebo design. Current e-cigarette users were randomized to use e-cigarettes that contained either nicotine or non-nicotine

solutions, and were independently instructed that the e-cigarette contained nicotine or non-nicotine, thus resulting in four experimental conditions: 1) told nicotine/given nicotine, 2) told non-nicotine/given nicotine, 3) told nicotine/given non-nicotine, and 4) told non-nicotine/given non-nicotine. From this, analyses of both independent and synergistic effects of nicotine dose and nicotine-related expectancies were conducted upon a range of dependent measures related to use motivation (see Figure 1).

Pharmacologic Manipulation	Instructional Set	
	<u>E-cigarette contains nicotine</u>	<u>E-cigarette does not contain nicotine</u>
<u>Nicotine</u>	True positive	False Negative, "Anti-Placebo"
<u>Non-Nicotine</u>	False positive, "Placebo"	True Negative

Figure 1: Experimental Design.

Specific Aim 1A and Hypotheses

Main effects of drug were hypothesized to affect physiological outcomes of nicotine use; that is, those receiving nicotine should report different physical responses to e-cigarette use as compared to those not receiving nicotine. More specifically, those participants who receive an e-cigarette containing nicotine may show greater attention, lower appetite, lower aversion and greater respiratory tract sensations compared to those who receive non-nicotine e-cigarettes. This

prediction is consistent with known effects of nicotine and previous balanced-placebo studies of nicotine and alcohol (i.e., Dawkins & Corcoran, 2014; Harrell & Juliano, 2012; Hull & Bond, 1986).

Specific Aim 1B and Hypotheses

Additionally, it was hypothesized that main effects of instruction would impact subjective effects of nicotine use; that is, those told they received nicotine should endorse different subjective responses to e-cigarette use as compared to those told they did not receive nicotine. More specifically, those participants who believe they are receiving an e-cigarette containing nicotine might report higher psychological reward, higher satisfaction, less desire to smoke/use e-cigarettes, and lower negative affect than those told they received a non-nicotine e-cigarette. This prediction is consistent with previous studies examining effects of expectancies on tobacco, alcohol, and e-cigarette use outcomes and subjective responses (i.e. Copp et al., 2015; Dawkins, Turner, Hasna, & Soar, 2012; Gottlieb, Killen, Marlatt, & Taylor, 1987; Hull & Bond, 1986; Juliano & Brandon, 2002; Tate et al., 1994).

The independent and synergistic effects of nicotine and instructional set were tested on all dependent variables. However, a priori hypotheses are limited to the above.

Secondary Aims

Participant characteristics, baseline expectancies about e-cigarettes, and e-cigarette dependence were further explored as moderator variables, as previous research and theory indicates that these factors may influence response to e-cigarette use. In particular, craving reduction expectancies and other specific expectancies, dependence, smoking status (current or former), and gender were tested as moderators of instructional set or drug manipulation. It was thought that expectancies would moderate the effects of instructional set in that these reflect

response expectancies that should be activated by stimulus expectancies, which then influence perceived outcomes. The degree to which the drug produces outcome effects may be impacted by level of dependence (due to either sensitization or tolerance effects); thus, dependence was predicted to moderate main effects of drug. Finally, differences in e-cigarette expectancies and nicotine dependence have been observed between smoking status and gender in previous research (e.g. Harrell et al., 2015; Piñeiro et al., 2016, Shiffman & Paton, 1999).

METHOD

Sample Size

Sample size analyses were conducted using G-power (Faul, Erdfelder, Lang, & Buchner, 2007). It was determined that a sample size of 128 (32 per group) was required for the analysis to achieve power of .80 for detecting main effects among the 4 groups, with a medium sized effect ($f = .25$) and a two-tailed alpha level of .05.

Participants

Interested participants were recruited through flyers at local vape shops and community locations, online advertisements, within-lab referrals, and the undergraduate psychology participant pool (SONA). A sample of 130 participants attended the laboratory session after meeting eligibility criteria: 1) At least 18 years old; 2) Current daily e-cigarette users (use at least once per day for the past 30 days, must use nicotine solutions, must like tobacco, menthol, or fruit flavor); 3) Smoking history of at least 100 lifetime cigarettes; 4) History of or current smoking rate of at least 1 cigarette per day for at least 30 days; 5) No current engagement in an *e-cigarette* cessation attempt; and 6) Not currently pregnant, attempting to get pregnant, or nursing (by self-report). A study flow diagram detailing participant recruitment and randomization can be seen in Figure 2.

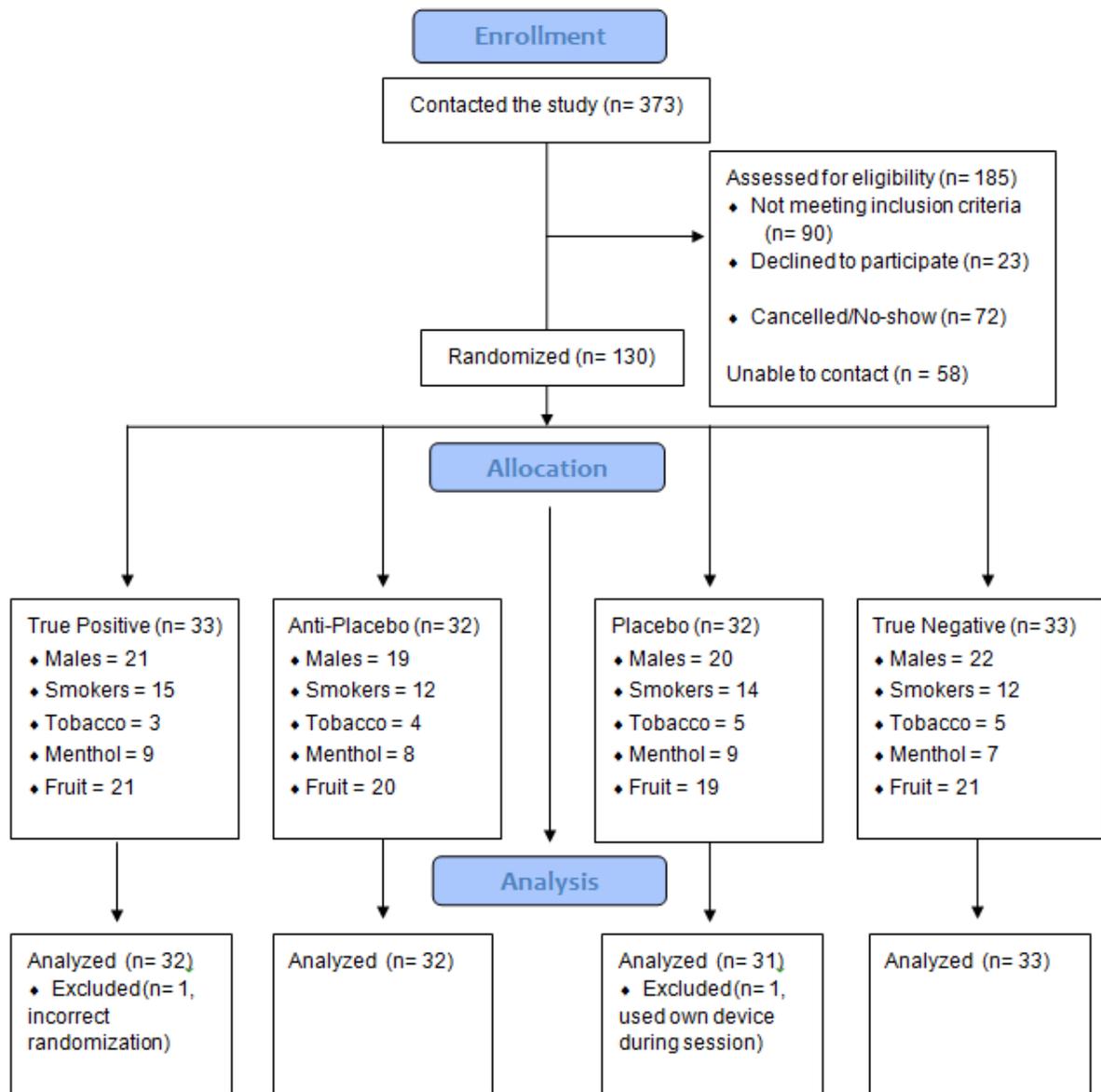


Figure 2. Study Flow.

Baseline Measures

Baseline and Demographic Questionnaire

Participants reported time since last meal, time since last cigarette (if current smoker), and time since last e-cigarette use. A research assistant also collected a carbon monoxide (CO) reading. Participants then completed questionnaires capturing basic demographic information, smoking history, and vaping history. Vaping history included questions pertaining to the individual's expectancies about general device characteristics.

Expectancies about E-Cigarettes

Participants' expectancies about the effects of e-cigarette use were measured with a modified version of the Smoking Consequences Questionnaire-Adult (SCQ-A; Copeland, Brandon, & Quinn, 1995). On this scale, participants are asked to consider the likelihood of a particular consequence on a scale of "0 / completely unlikely" to 9 "completely likely." The original questionnaire was developed to assess expectancies about the reinforcing effects of cigarettes in adults, and the items load onto ten factors: Negative Affect Reduction, Stimulation/State Enhancement, Health Risk, Taste/Sensorimotor Manipulation, Social Facilitation, Weight Control, Craving/Addiction, Negative Physical Feelings, Boredom Reduction, and Negative Social Impression. In the present study, one item from each of the original factors was included, and items were modified to ask about using e-cigarettes instead of smoking cigarettes. Additionally, questions about satisfaction, stress reduction, and attention were added. This modified version has been successfully implemented in previous research to assess expectancies of e-cigarette use in comparison to expectancies about cigarette smoking and NRT (Harrell et al., 2014) and showed internal consistency in the current study (coefficient $\alpha = 0.73$).

Dependence

Dependence on e-cigarettes was measured using the Penn State Electronic Cigarette Dependence Index (Foulds et al., 2014). This questionnaire was derived from the Cigarette Dependence Index, which was developed using items and constructs from other cigarette dependence measures that were found to be the most predictive of future smoking. The questionnaire was modified for e-cigarette use and has been tested on e-cigarette users to assess levels of e-cigarette dependence as compared to cigarette dependence. Scores range from 0-20, with higher scores indicating higher dependence ($\alpha = 0.70$). Additionally, cigarette dependence (past or present) was measured with the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), included in the smoking history. Scores on this measure range from 1-10, with higher scores indicating greater dependence ($\alpha = 0.56$ for current smokers; $\alpha = 0.66$ for former smokers).

Dependent Variables

The following measures were assessed before and after the ad-lib “vaping” session, with the exception of the modified mCEQ and RVIP which were only administered after.

Desire to Smoke and Desire to Use E-cigarettes

The desire to smoke and the desire to use e-cigarettes were measured both pre- and post- ad-lib session using a 3-item adaptation of the Questionnaire of Smoking Urges-Brief (QSU). The QSU is a 10-item questionnaire that measures desire and intentions to smoke based on relief of negative symptoms and anticipation of positive effects (Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991). However, there is evidence that an adaptation of this measure, which utilizes 3 items assessing urge to smoke, is equally valid in measuring desire to smoke (Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996). In the present study, this shorter version was

administered in its original form as well as a modified version for e-cigarettes. On each item, participants are asked to report the degree to which they agree with a particular statement from “0 – strongly disagree” to “6 – strongly agree,” for a score range of 0-24. The modified version in the present study showed excellent reliability ($\alpha = 0.91$), as did the original version ($\alpha = 0.92$).

Mood

The maintenance of cigarette smoking behaviors can be attributed in part to mood regulation (Brandon, 1994). In the first balanced-placebo design with cigarettes, it was found that both nicotine and expectancies impacted the reduction of a negative mood state (Juliano & Brandon, 2002). Because of the close-knit relationship between smoking and mood regulation, it is possible that this relationship also exists among e-cigarette use. The Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988) was administered to evaluate current mood state pre- and post- ad-lib session. This measure assesses both positive and negative dimensions of mood as scores for each range from 10-50, with higher scores indicating a greater degree of that particular mood. This measure showed good internal consistency throughout the session (Positive pre-test $\alpha = 0.86$, post-test $\alpha = 0.90$; negative pre-test $\alpha = 0.82$, post-test $\alpha = 0.85$).

Appetite

Animal studies have suggested that nicotine has a metabolic effect on appetite suppression (Winders & Grunberg, 1990), and this is reflected in smokers' expectancies (Brandon et al., 1999). To assess changes in appetite pre- and post- ad-lib session, a Visual Analogue Scale (VAS; Flint, Raben, Blundell, & Astrup, 2000) was used with good internal consistency (pre-test $\alpha = 0.89$; post-test $\alpha = 0.85$). This scale has been successfully used in previous research to determine changes in appetite among smokers (Jessen, Buemann, Toubro, Skovgaard, & Astrup, 2005). Scores range from 0-285, with higher scores indicative of increased appetite.

Reinforcement from E-cigarettes

Following the ad-lib session, participants rated how the e-cigarette made them feel on several dimensions. The Modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al., 2007) was designed to measure subjective immediate effects of cigarette smoking. These effects include Satisfaction (3 items; $\alpha = 0.87$ in current study), Psychological Reward (5 items; $\alpha = 0.85$ in current study), Aversion (2 items; $\alpha = 0.66$ in current study), Enjoyment of Respiratory Tract Sensations (1 item), and Craving (1 item). In the present study, the questionnaire was also modified for e-cigarettes and administered to assess the degree to which participants experience reinforcing effects of using the e-cigarette, and it showed good reliability on the subscales. Scores for each item range from “1 – not at all” to “7 – extremely.”

Sustained Attention

Smoking has been shown to improve short-term sustained attention (Heishman, Kleykamp, & Singleton, 2010). Therefore, the degree to which this effect occurs with e-cigarettes, as driven by nicotine versus expectancies, was assessed using the Rapid Visual Information Processing Task (RVIP; Wesnes & Warburton, 1983). This task has been shown to be sensitive to both the effects of nicotine and stimulus response expectancies (Heishman et al., 2010; Juliano, Fucito, & Harrell, 2011) and has been used in previous studies to assess cognitive changes in smokers during balanced-placebo tasks (Harrell & Juliano, 2012; Juliano et al., 2011).

The task was administered via E-Prime (Psychology Software Tools, Inc.). Participants viewed a series of single digits presented at a rate of 100 digits per minute for approximately 4 minutes, which is sufficient time to detect effects due to nicotine withdrawal (Hendricks et al., 2006). Participants were told to respond (pressing the spacebar) to a specific target series of three consecutive odd or three consecutive even digits. Reaction time was recorded, with a “hit”

defined as correctly identifying the target within 1,500ms. Targets appear 8 times per minute with 8-36 digits appearing between each target. Response sensitivity was calculated using the individual's hit rate (hr; correct responses) and false alarm rate (far; incorrect responses) in the formula $0.5 + [(hr - far) + (hr - far)^2] / 4*hr*(1 - far)$ (Sahgal, 1987), which has been utilized by several studies assessing the effect of nicotine on cognitive performance (e.g. Foulds et al., 1996; Harrell & Juliano, 2012; Juliano et al., 2011). This is a measure of accuracy provides a more comprehensive representation of meaningful, voluntary attention than reaction time (Prinzmetal, McCool, & Park, 2005). For the final analysis, 9 participants were removed (1 = missing data, 8 = outliers) and a reciprocal transformation was performed on the data to reduce negative skew and kurtosis.

Nicotine Dosing Estimate

Participants completed a brief questionnaire post ad-lib session asking them to estimate the nicotine dose of the provided e-cigarette (0mg/ml, 6mg/ml, 12 mg/ml, 18 mg/ml, 24mg/ml). As a mask, participants also rated how much they enjoyed the e-cigarette, how likely they are to recommend the e-cigarette, and other subjective evaluations. Participants also rated the e-cigarette in comparison to their usual device to gauge the similarity of their vaping experience in the laboratory.

Number of E-cigarette Puffs

After completing the ad-lib vaping session, the research assistant recorded the number of puffs taken by the participant as measured by the display on the e-cigarette.

Apparatus

E-cigarette

Participants were provided with an “eGo LCD MEGA” 3.6-4.2 Volt, 1100 mAh battery with a 1ml “eGo+” 2.8-Ohm, 510-style clearomizer (transparent tank for the liquid solution that is connected to a heating coil). This style setup is “second generation” and familiar among vapers, which is an advantage over other studies utilizing the less popular “cig-a-like” models. Each participant received a new mouthpiece and tank, not only for hygienic purposes, but because the heating coils weaken over time with continued use. The particular battery used contains an LCD display showing number of puffs, which aided compliance with the ad-lib instructional set (as described in the procedure). Clearomizers were filled with solution (nicotine or non-nicotine) by an individual who had no participant contact, thus allowing research staff to be blind to actual nicotine content based on randomization.

Solution

The solution used was a 50% vegetable glycerin (VG), 50% propylene glycol (PG) liquid. Nicotine content was either 0mg/ml or 12 mg/ml, with the latter having produced similar plasma nicotine concentrations (as measured in venous blood samples) as traditional cigarettes in previous studies (Ramôa et al., 2015; Russell, Wilson, Patel, Feyerabend, & Cole, 1975; Yan & D’Ruiz, 2014). One critique of balanced placebo designs in the alcohol field is the difficulty to make a feasible placebo drink (George et al., 2012). This being said, careful consideration was made in determining the constituents of the nicotine solution used for this study. In terms of the spectrum of nicotine content available, this level is mid-range, and thus, could potentially be detected depending on the participant’s own nicotine content experience. Although other VG/PG ratios exist, conversations with local vape shop employees indicated that a higher ratio of PG

creates a stronger “throat hit,” and because of this, is preferred for those transitioning from smoking to vaping. Following successful cigarette reduction or cessation, many users will opt for a higher ratio of VG, which reduces the strength of the “hit” and increases vapor production. Therefore, using a mid-range nicotine concentration with a 50/50 VG/PG ratio allowed for participants to experience the effects of nicotine while also allowing the experimental manipulation to be masked. Finally, in addition to tobacco and menthol flavors traditionally offered in laboratory studies involving cigarettes, a fruit flavor option was also used. Survey research shows that non-cigarette flavors are popular among vapers (Berg, 2016); therefore, this additional flavor option was added to increase the familiarity of the ad-lib product (thus aiding instructional compliance) as well as to increase generalizability.

In line with current NIH guidelines on authentication of chemical resources (Reviewer Guidance on Rigor and Transparency: Research Project Grant and Mentored Career Development Applications, 2016), the quality of the solution was also tested. Some studies show that nicotine solutions available for purchase by the general public may be mislabeled in terms of constituents or nicotine content (Trehy et al., 2011). With this concern in mind, the solution used in this study was a custom-made “research blend” that was then tested by the manufacturer for dose accuracy (Avail Vapor, LLC). Upon receipt of the solution, it was then tested a second time by the supporting institution (Moffitt Cancer Center Proteomics Core) using mass spectrometry and liquid chromatography to ensure comparable results to those provided by the manufacturer. Results confirmed that the 0mg/ml solutions did not contain nicotine; however, nicotine content results varied between the two labs, and were inconsistent with the label. The vendor reported the tobacco flavor to be 11.82 mg/ml, whereas the institution lab tested it at 10.3 (± 0.8) mg/ml, a 14% difference from the original label (12 mg/ml). Similarly, the menthol flavor was reported by

the vendor to contain 11.94 mg/ml nicotine, and the institution lab concluded it to have 11.2 (± 1.7) mg/ml, 7% lower than originally labeled. Finally, the original batch of the fruit flavor was reported by the vendor to be 12.11 mg/ml, but the institution lab found this batch to be 31% lower than originally labeled at 8.3 (± 0.5) mg/ml; and in response to this large discrepancy, a replacement batch was requested. This second batch was tested by the vendor to be 12.25 mg/ml and tested by the institution to contain 10.0 (± 0.8) mg/ml, which was a 17% difference in the original label. Thus, all nicotine flavors were verified to contain at least 10.0 mg/ml.

Procedure

Telephone Screening

All individuals were screened via telephone. Qualified, scheduled participants were asked to abstain from using e-cigarettes and combustible cigarettes for three hours prior to the session. As an attempt to increase adherence, participants were notified that a breath CO reading would be administered upon arrival. Participants were also offered a text message abstinence reminder three hours before the appointment, which most accepted. At this time, participants selected their flavor preference (tobacco, menthol, or fruit) for the session. Participants were notified of compensation for the study (\$30 or 3 SONA points).

Consent

The experimenter provided the participant with a copy of the consent form, which included a brief description of the study and explained the purpose, risks, benefits, rights, and confidentiality of the study. It is especially important in balanced placebo designs to reduce threats to internal validity (George et al., 2012). As such, participants were informed that this was a study of nicotine and e-cigarettes, and they may or may not receive nicotine during the procedure. This cover story aligns well with established recommendations for balanced placebo

designs in the alcohol field, and allows participants an accurate description of the study while masking the true purpose within ethical guidelines (Marlatt & Rohsenow, 1980).

Qualification and Randomization

After signing consent, participants qualified to participate through self-reported abstinence from cigarettes and e-cigarettes for at least 3 hours prior to arrival. Once these requirements were satisfied, participants were then randomized for both instructional set and nicotine content. Randomization was pre-determined using a random number generator on Microsoft Excel, and used a 4-block pattern with stratification based on gender (male or female), cigarette smoking status (current or former), and flavor preference (tobacco, menthol, or fruit). The nicotine content in the e-cigarette and instructional randomization were prepared prior to the study session by a lab member with no participant involvement.

Administration of Baseline Questionnaires

Participants completed demographic and baseline measures as follows: Demographic and Smoking History Questionnaire, modified SCQ-A, and Penn State Electronic Cigarette Dependence Scale.

Ad-lib Vaping Session

Participants completed the first administration of dependent measures (QSU [current smokers] and modified QSU, PANAS, and VAS). Participants were then prompted to try an e-cigarette, which was provided by the experimenter in a box labeled “Nicotine” or “No nicotine,” consistent with the instructional set manipulation. Depending on prior randomization results, the research assistant told the participant that the e-cigarette contained either a nicotine solution (no specific dose mentioned) or a non-nicotine solution. Participants were instructed to take at least 10 puffs over the 10 minute session, noting that the e-cigarette had a puff counter on it. Prior

research has indicated that after 10 puffs using a 12mg/ml liquid nicotine solution (which would be used if randomized to that condition), nicotine plasma levels are similar to that of traditional cigarettes (Ramôa et al., 2015). During this session, participants were monitored by video to ensure instructional compliance.

Post-Vaping Session Measures

After the ad-lib session, the following dependent measures will be administered: Modified mCEQ, QSU (if current cigarette smoker) and modified QSU, PANAS, VAS, RVIP, and Nicotine Dosing Estimate Form.

Compensation and Debriefing

Participants were debriefed and provided compensation for his/her time and travel.

Data Analysis Plan

To test group equivalence on demographics, nicotine dependence, and other baseline variables, a series of chi-squares or analyses of variance (ANOVAs) were conducted, comparing the conditions. Next, to test the hypotheses in Aims 1 and 2, condition groups were compared using factorial ANOVA or analysis of covariance (ANCOVA; if a pre- test score was used as a covariate).

Several expectancy and baseline characteristics were explored as moderators to evaluate if participant characteristics affected the main effects of the drug manipulation as well as the instructional manipulation. Hierarchical liner regression was used, entering the pre-test score (if applicable) as the first step, the manipulation variable as the second step (instructions or nicotine content), the moderator variable (expectancy variable, dependence, smoking status, or gender) as the third step, and lastly, the moderator X manipulation interaction. Post-hoc simple effects

analyses were used to assess trends between moderator variable groups, with pre-test score included as a covariate in step 1 and drug or instructional manipulation added in step 2.

Finally, significant differences in moderator groups were followed up by exploratory comparisons of expectancies using independent samples t-tests.

RESULTS

Participant Characteristics

Two participants were removed from final analyses (one for instructional non-compliance, one for incorrect randomization) for a final sample size of 128. Participants were coded as current smokers if they reported smoking cigarettes at least once per week. Participant demographic and characteristic information can be seen in Tables 1 and 2, respectively (see pages 28-29). Overall, the sample was diverse and representative of the geographic area of recruitment. It should be noted that there was a great deal of variability in estimated e-cigarette use patterns. Results from chi-squared tests and ANOVAs did not show any significant differences between conditions on any demographic, baseline, or pre-test variables. Mean puff counts did not differ between conditions ($F [3, 126] = 2.13, p = 0.10$; True Positive $M = 21.38, SD = 9.18$; Anti- Placebo $M = 18.77; SD = 9.2$, Placebo $M = 20.61, SD = 10.14$; True Negative $M = 26.00, SD = 17.11$). Current smokers and former smokers were compared across conditions, with differences found in e-cigarette dependence, current or past cigarette dependence, and several other e-cigarette use characteristics.

Manipulation Effects

The independent and synergistic effects of both nicotine content and instructional set on the hypothesized dependent variables were tested with ANOVAs, or ANCOVAs, if controlling for pre-ad-lib session scores. Results are shown in Table 3 (see page 30).

Table 1. Participant Demographics (N=128).

Variable	Description	Mean or N	% or SD
Age	(range 18-76)	36.4	13.79
Gender	Male	80	62.50%
	Female	48	37.50%
Race	American Indian / Alaska Native	1	0.80%
	Asian	3	2.30%
	Native Hawaiian / Pacific Islander	1	0.80%
	Black / African American	15	11.70%
	White / European Origin	106	82.80%
	Did not report	2	1.60%
Ethnicity	Hispanic / Latino	20	15.60%
	Non-Hispanic	108	84.40%
Marital Status	Single	77	60.20%
	Married	30	23.40%
	Separated	2	1.60%
	Divorced	16	12.50%
	Widowed	2	1.60%
	Did not report	1	0.80%
Sexual Orientation	Identify as LGBT+	16	12.50%
	Straight	111	86.70%
	Did not report	1	0.80%
Education	Less than high school	7	5.50%
	High School	25	19.50%
	Some College	39	30.50%
	Tech School / Associate's	37	28.90%
	4-year College Degree	13	10.20%
	Beyond 4-year Degree / Professional Degree	7	5.40%
Income	Under \$10,000	28	21.90%
	\$10,000 - \$29,999	36	28.12%
	\$30,000 - \$49,999	30	23.43%
	\$50,000 - \$69,999	14	10.94%
	Above \$70,000	19	14.84%

Note: No significant differences between conditions were found for any of the variables.

Table 2. Participant Smoking and Vaping Characteristics.

	Full sample (N=128)	Current smokers (N=52)	Former smokers (N=76)
% Daily smoking (current or past)	76.56%**	51.90%	92.10%
Cigarettes per day (current or past): <10	50%	69.20%	36.80%
Cigarettes per day (current or past): 11-20	30.50%	21.15%	36.80%
Cigarettes per day (current or past): >20	19.50%*	9.61%	26.31%
Mean number of daily e-cigarette uses (SD)	36.5 (53.36)	26.66 (42.4)	43.91 (59.6)
Mean minutes per e-cigarette use session (SD)	7.82 (6.71)	8.32 (7.57)	7.10 (5.29)
Mean puffs per e-cigarette use session (SD)	9.28 (6.70)	9.84 (5.78)	8.70 (7.57)
% reporting vaping continuously all day (SD)	46.90%**	34.60%	65.80%
% Using 3 rd generation “mod” devices	65.6%	51.9%	75%
Mean nicotine content of solution in personal device (mg/ml)	8.80 (7.51)*	10.57 (8.07)	7.71 (6.98)
Flavor used most often:			
Tobacco	10.90%	17.30%	6.60%
Menthol	21.10%	21.20%	21.10%
Fruit	41.40%	40.40%	42.10%
Other (e.g. custard, dessert, beverages)	22.70%*	11.50%	30.30%
Reported e-cigarette initiation to quit smoking	68%*	50%	80.30%
Reported past e-cigarette cessation attempt	21.90%	17.30%	25%
Reported no plans to reduce vaping	39.80%	34.60%	43.40%
Flavor requested for ad-lib session:			
Tobacco	11.70%	17.30%	7.89%
Menthol	25%	25%	25%
Fruit	63.30%	57.60%	67.10%
Mean EDCI	10.05 (4.66)**	8.44 (5.10)	11.15 (4.0)
Mean FTND (current or past)	4.50 (2.89)**	3.69 (3.28)	5.05 (2.45)

Note: In comparing current versus former smokers, * $p < .05$, ** $p < .01$. No significant differences were found between conditions on these variables.

Table 3. Manipulation Effects.

Variable	Adjusted means				Group means		Group means		F (Nicotine)	F (Instruction)	F (Nicotine X Instruction)
	True Positive	Placebo	Anti- Placebo	True Negative	Nicotine	No Nicotine	Told Nicotine	Told No Nicotine			
Modified mCEQ- Enjoyment of respiratory tract sensations	3.91	3.26	3.13	4.12	3.52	3.69	3.58	3.62	.26	.01	5.81*
RVIP sensitivity	1.65	1.59	1.59	1.51	1.62	1.56	1.62	1.55	3.21 [†]	3.42 [†]	.06
Modified mCEQ- Aversion	3.31	3.07	2.59	3.03	2.95	3.05	3.19	2.81	.08	1.22	1.01
VAS - hunger	121.06	125.10	127.67	119.40	124.37	122.25	123.08	123.53	.05	.00	.424
QSU- smoke	4.45	3.16	6.93	7.62	5.65	5.69	3.88	7.21	.58	7.895**	.628
Modified QSU-vape	5.00	8.16	9.69	8.60	8.20	7.53	6.24	9.45	1.14	6.86**	4.80*
Modified mCEQ- Psychological reward	19.81	14.03	15.66	17.46	17.73	15.79	16.97	16.57	2.31	.079	8.37**
Modified mCEQ- Satisfaction	14.94	12.84	12.25	13.27	13.59	13.06	13.89	12.76	.359	1.58	3.02 [†]
PANAS- positive	31.79	30.82	29.88	30.10	30.83	30.46	31.30	29.99	1.846	.148	.374
PANAS- negative	13.06	12.41	12.94	12.77	13.00	12.59	12.74	12.86	.593	.051	.207

Note: [†] $p < .10$, * $p < .05$, ** $p < .01$. Modified mCEQ = modified Cigarette Evaluation Questionnaire, modified for e-cigarettes. RVIP = Rapid Visual Information Processing task. VAS = Visual Analogue Scale. QSU = Questionnaire of Smoking Urges-Brief- Urge factor. PANAS = Positive and Negative Affect Scale.

Aim 1

First tested were the variables hypothesized to be affected by the nicotine manipulation (appetite, aversion, enjoyment of respiratory tract sensations, and sustained attention). A series of 2X2 ANOVAs showed no main effects, but revealed a significant interaction between nicotine content and instructional set on the Enjoyment of Respiratory Tract Sensations factor of the modified mCEQ. Post-hoc comparisons revealed that the Placebo condition produced significantly lower scores ($M = 3.26$) than the True Negative condition ($M = 4.12$; $F [1, 62] = 4.07, p < .05$). In addition, participants in the Anti-Placebo condition ($M = 3.12$) had significantly lower scores than the True Positive condition ($M = 3.91$; $F [1, 62] = 2.16, p > .05$) and the True Negative condition ($F [1, 63] = 4.18, p < .05$). Results are plotted in Figure 3 (see pages 32). A marginally significant main effect of nicotine was found on sustained attention as measured by RVIP sensitivity ($F [1, 115] = 3.21, p = .08$), in addition to a marginally significant main effect of instruction ($F [1, 115] = 3.42, p = .07$); no significant interaction was found. As seen in Table 3, both actual nicotine delivery and the nicotine delivery instructional set yielded slightly greater RVIP scores. Additional tests failed to produce significant main effects or interactions on appetite (VAS; with the pre-test score as a covariate) and aversion (from modified mCEQ).

Gender was tested as a moderator of these outcomes. In terms of appetite as measured by the VAS, a nicotine X gender observation was observed ($\beta = .60, F [1, 123] = 5.72, p < .05$). There was a marginally significant effect of nicotine among females, in that those receiving nicotine reported greater VAS scores ($M = 128.20, SD = 82.71$)¹ than those not receiving nicotine ($M = 110.78, SD = 82.95$; $\beta = .18, F [1, 45] = 2.93, p = .09$). Among males, the

¹ Means presented for moderation analyses post-hoc simple effects are unadjusted.

difference between those receiving nicotine ($M = 123.10$, $SD = 73.71$) and those not receiving nicotine ($M = 127.41$, $SD = 84.43$) was not as pronounced, $\beta = -.10$, $F(1, 77) = 2.13$, $p = .15$.

Males and females did not differ on appetite control expectancies.

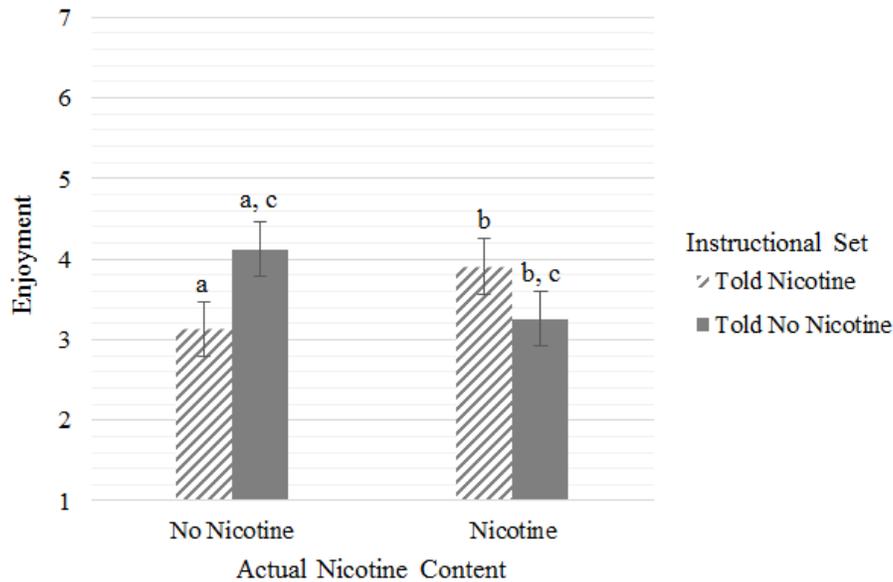


Figure 3. Manipulation Effects on Modified mCEQ – Enjoyment of Respiratory Tract Sensations.

Note: Interaction $p < .05$. Bars with same subscripts represent paired comparison differences at $p < .05$. Error bars are standard error of the mean.

A nicotine X gender interaction was observed on RVIP sensitivity ($\beta = .94$, $F[1, 115] = 5.98$, $p < .05$), with post-hoc analyses showing that sustained attention increased for females when receiving nicotine ($M = 1.65$, $SD = 0.21$; $\beta = .40$, $F[1, 39] = 7.35$, $p = .01$) compared to those not receiving nicotine ($M = 1.46$, $SD = 0.24$), but this effect was not found for males (both $M_s = 1.6$, SD [Nicotine] = 0.19, SD [Non-Nicotine] = 0.19; $\beta = .01$, $F[1, 76] = 0.01$, $p = .93$). No differences in concentration expectancies were found between genders.

E-cigarette dependence (as measured by the ECDI) and smoking status (smoker or former smoker) were tested as moderators of nicotine effects on variables presented in Hypothesis 1A. Results failed to show significant interaction effects on any dependent variables.

Aim 2

Next tested were the variables hypothesized to be affected by instructional set (desire to smoke and vape, affect, psychological reward, and satisfaction). First, desire to smoke was tested among current smokers only. A 2X2 ANCOVA (using pre-test QSU scores as a covariate) showed a main effect of instruction on desire to smoke as measured by the QSU, $F [1, 47] = 7.90, p < .01$; covariate-adjusted post-test scores were lower among those told they received nicotine ($M = 3.88$) than those told they did not receive nicotine ($M = 7.21$). No main effect of nicotine dose or interaction was found (see Figure 4).

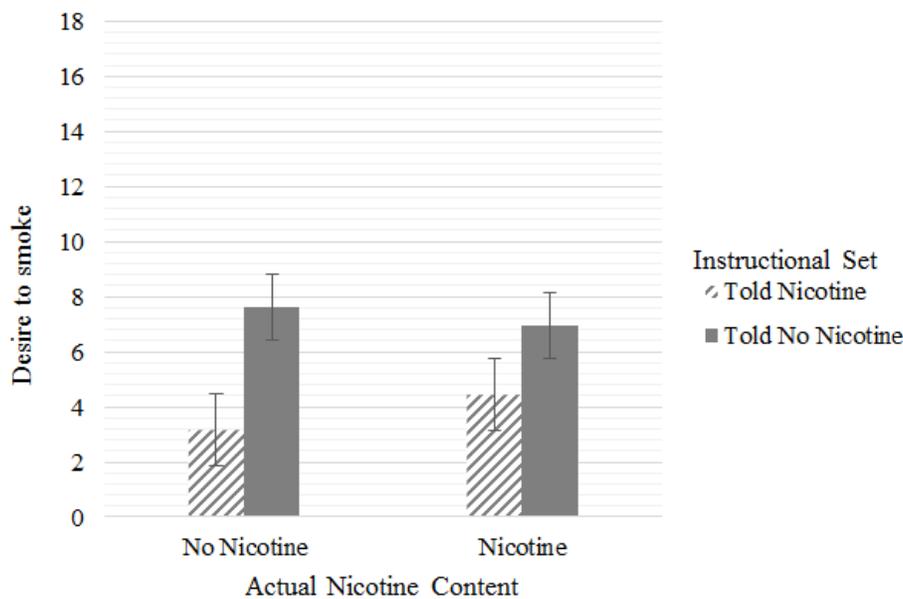


Figure 4. Manipulation Effects on Desire to Smoke Among Current Smokers (N = 52).

Note: Main effect of instruction significant at $p < .01$. Scores presented are adjusted by pre-test QSU covariate = 11.62. Error bars are standard error of the mean.

Gender was tested as a moderator of the hypothesized outcomes of the instructional manipulation, and an instruction X gender interaction was found on desire to smoke ($\beta = 1.23$, $F [1,47] = 6.68$, $p < .05$) among current smokers. Results from post-hoc simple effects analyses showed that for males, being told that they received nicotine reduced cravings to smoke ($M = 1.92$, $SD = 2.33$; $\beta = -.56$, $F [1,25] = 17.37$, $p < .001$) compared to those told they did not receive nicotine ($M = 9.13$, $SD = 5.73$). However, the same effect was not observed for females in that those told they received nicotine ($M = 6.18$, $SD = 5.95$) did not differ from those told they did not receive nicotine ($M = 5.00$, $SD = 4.32$; $\beta = -.02$, $F [1,21] = 0.01$, $p = .93$).

To further explore the aforementioned gender differences, the full model was tested with gender as a moderator. That is, a drug X instruction X gender ANCOVA was conducted on desire to smoke using the pre-test score as a covariate. Results replicated those of the initial moderation analyses, as a gender X instruction interaction was observed, $F [1, 43] = 6.18$, $p < .05$. No gender X nicotine interaction nor gender X instruction X nicotine interaction was found. Moreover, independent samples t-tests showed that male and female smokers did not differ on craving reduction expectancies. Among the total sample, however, males had higher craving reduction expectancies ($M = 8$, $SD = 2$) than females ($M = 7$, $SD = 2$; $t (126) = 2.58$, $p < .05$).

Desire to vape was then tested among the full sample, using the modified QSU pre-test score as a covariate. We found a main effect of instruction on desire to vape in addition to an interaction effect among the total sample (see Figure 5). Post-hoc comparisons revealed that the True Positive condition (estimated $M = 5.01$) had significantly lower scores than all other conditions: the True Negative condition (estimated $M = 8.60$; $F [1, 62] = 7.26$, $p < .01$), the Placebo condition (estimated $M = 8.16$; $F [1, 60] = 4.39$, $p < .05$), and the Anti-Placebo condition (estimated $M = 9.69$; $F [1, 61] = 13.87$, $p < .001$).

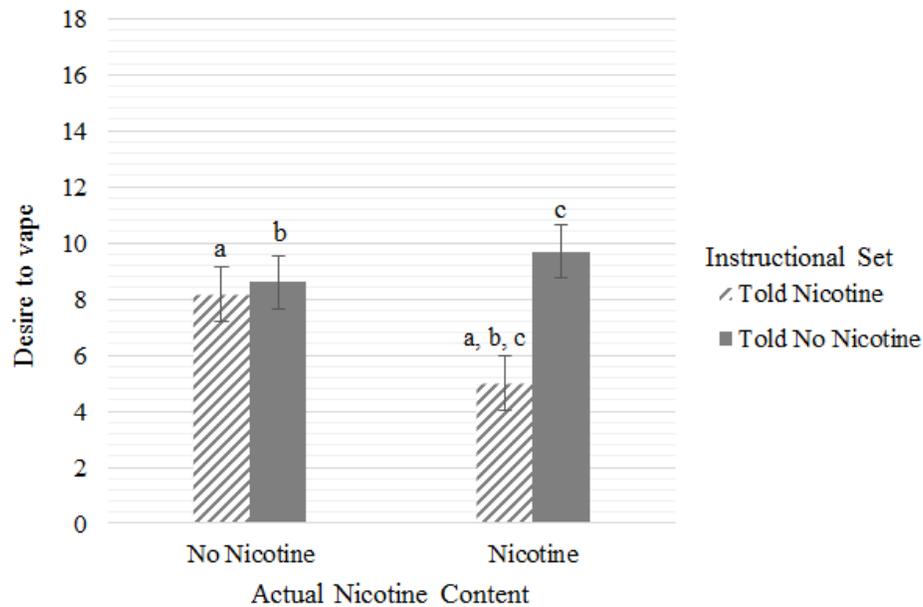


Figure 5. Manipulation Effects on Desire to Vape.

Note: Interaction $p < .05$. Bars with same subscripts represent paired comparison differences at $p < .05$. Scores presented are adjusted by pre-test modified QSU covariate = 12.96. Error bars are standard error of the mean.

An additional ANCOVA on the Psychological Reward factor of the modified mCEQ failed to yield main effects, but produced a significant interaction, plotted in Figure 6. Post-hoc comparisons among conditions revealed that the Placebo condition had lower scores (estimated $M = 14.03$) than the True Positive condition (estimated $M = 19.81$; $F [1, 61] = 9.54, p < .01$). In addition, a significant difference was found between the True Positive condition and the Anti-Placebo condition (estimated $M = 15.66$; $F [1, 62] = 4.51, p > .05$). There was a marginally significant difference between the Placebo condition and the True Negative condition (estimated $M = 17.46$; $F [1, 62] = 3.86, p = 0.54$). Finally, of note, results revealed a marginally significant interaction on Satisfaction as measured by the modified mCEQ ($F [1, 124] = 3.02, p = .09$), with the True Positive condition yielding the greatest satisfaction from vaping.

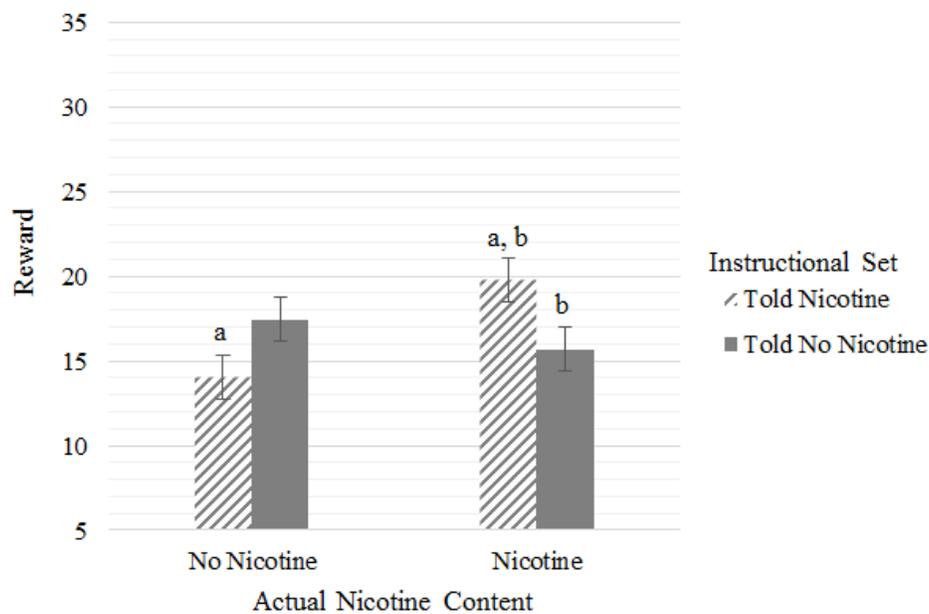


Figure 6. Manipulation Effects on Psychological Reward.

Note: Interaction $p < .05$. Bars with same subscripts represent paired comparison differences at $p < .05$. Error bars are standard error of the mean.

Additional Tests of Moderation

The only moderations by gender upon main effects were those reported above. We first tested craving reduction expectancies (as measured by the modified SCQ item stating “Vaping will satisfy my nicotine cravings”) as a moderator of instructional set on all variables listed under Hypothesis 1B. All results were null, with the exception of the expectancies X instruction interaction on Satisfaction scores ($\beta = .98$, $F [1,123] = 4.42$, $p < .05$). Post-hoc regressions showed that among those told they did not receive nicotine, lower expectancies predicted higher Satisfaction scores ($\beta = -.30$, $F [1,63] = 6.18$, $p < .05$). No significant findings were shown for those told they received nicotine ($\beta = 0.07$, $F [1,161] = 0.34$, $p = .56$).

Next, smoking status was tested as a moderator of the manipulation effects and related outcomes. A smoking status X instruction interaction was found on Positive Affect ($\beta = -0.52$, $F [1,122] = 4.25$, $p < .05$). Results indicated that for current smokers, the instructional set manipulation had a marginally significant effect on post-test PANAS scores, ($\beta = .18$, $F [1,48] = 3.03$, $p = .09$) in that the told-nicotine manipulation increased positive affect among smokers following the ad-lib session. However, there was no such effect among former smokers.

The satisfaction expectancy item failed to moderate instruction effects on the Satisfaction factor of the modified mCEQ. Additionally, the affect regulation expectancy item did not moderate the instructional manipulation on either positive or negative affect, as measured by the PANAS. Because of the trending main effect of instructional set on RVIP sensitivity, concentration expectancies were tested as a moderator of the instructional set manipulation on this outcome. However, results were also nonsignificant.

Nicotine Dosing Estimate

Figure 7 shows participants' mean estimates of their nicotine doses. A 2x2 ANOVA showed main effects of both instruction ($F [1, 124] = 47.17$, $p < .001$) and drug content ($F [1, 124] = 15.71$, $p < .001$) on estimated nicotine content; however, the interaction did not reach significance ($F [1, 124] = 3.88$, $p = .051$). Those told they were receiving nicotine had a higher estimated nicotine guess ($M = 10.98$) than those told they were not receiving nicotine ($M = 4.12$). Similarly, higher nicotine guesses were reported among those receiving nicotine ($M = 9.50$) versus those not receiving nicotine ($M = 5.50$).

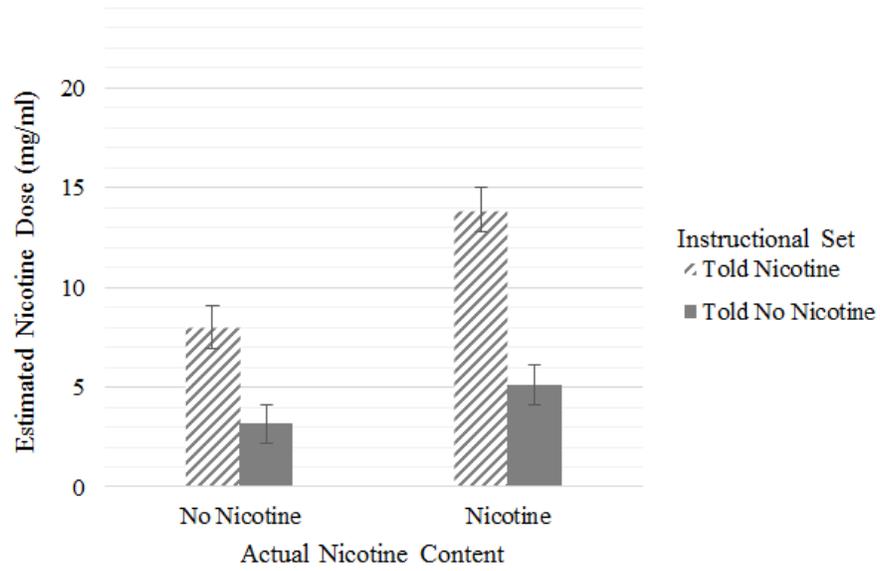


Figure 7. Manipulation Effects on Nicotine Dose Estimate.

Note: Main effects of instructional set ($p < .001$) and nicotine dose ($p < .001$). Error bars are standard error of the mean.

DISCUSSION

A great deal of controversy surrounds e-cigarettes, as little is known about the addictive potential of these products. In the present study, a balanced placebo design was utilized to parse the independent and synergistic influences of both the drug content and expectancies on outcomes of e-cigarette use. In an attempt to explore driving factors of e-cigarette use that might be impacted by drug content and expectancies, a number of outcome variables were tested. It was hypothesized that effects of nicotine would be found in physiological outcomes, whereas expectancy effects would impact psychological responses. Although no significant main effects of drug content were observed, the instructional set manipulation elucidated a significant main effect on both desire to smoke and desire to vape, though the former was driven solely by males. Additionally, significant interactions emerged within the psychological reward and enjoyment of respiratory tract sensation outcomes. In contrast to hypotheses, dependence did not moderate the main effects or overall manipulations. However, expectancy variables and smoking status moderated some effects, as did gender.

Desire to Smoke and Vape

Most conceptualizations of addictive drug use consider the effects of the drug itself, especially in terms of dependence and alleviating a state of withdrawal (Hughes et al., 1984). However, psychological factors can also influence the level of dependence on a particular drug, including the desire to use the drug (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). The results of this study provided continued support that cravings to use a drug are not solely driven

by the desire to relieve physical withdrawal. Participants in the True Positive condition and the Placebo condition, both of whom were told that they received nicotine, reported lower scores on the QSU and modified QSU. This provides evidence that these desires can be largely driven by beliefs about the drug content. These results are consistent with the findings of previous balanced-placebo designs with cigarettes, in that the expectancies about the drug alone reduced cravings regardless of actual nicotine dose (Juliano & Brandon, 2002; Perkins, Sayette, Conklin, & Caggiula, 2003). These results present some evidence to support the notion that reductions in desire to smoke via e-cigarette use may not be driven solely by nicotine, but also by the activation of expectancies associated with the belief that one is receiving nicotine.

Of interest within the results of this study is that the effects of instruction emerged more clearly within the desire to smoke outcomes in comparison to desire to vape. The interaction found on desire to vape provides evidence that e-cigarette craving reduction is a product of both the relief of withdrawal symptoms through drug administration as well as expectancies. Of particular interest is the True Positive condition reporting significantly lower urges to vape than any of the other conditions. The aforementioned interactions continue to support a formulation of drug use behavior that includes both pharmacological effects as well as cognitive expectancies.

In addition, the gender moderation effect observed on desire to smoke outcomes is notable in that only males showed effects of the instructional set manipulation. It has been observed in previous studies that women may be less physiologically responsive to nicotine administration, more likely to smoke for social or tactile, habitual reasons, and that nicotine replacement therapy may be less effective for females (Perkins & Scott, 2008; Perkins, 1996). Interestingly, in the present study, females showed greater effects of the nicotine dosing manipulation than males on reported appetite and attentional performance (RVIP). Furthermore,

recent research has shown that males have stronger e-cigarette craving reduction expectancies than females (Piñeiro et al., 2016). For these reasons, women may be less likely to develop expectancies that nicotine reduces cravings, and thus, they might be less responsive to an instructional set manipulation designed to activate such expectancies. Yet, in the present sample, no gender differences among smokers emerged on the relevant expectancy scale (among the full sample, however, males reported higher craving reduction expectancies). In summary, findings indicated that females were more sensitive to actual nicotine with respect to appetite and attention, but male smokers were more responsive to the instructional set manipulation with respect to craving reduction. These results add to the already complex pattern of tobacco-related gender differences in the literature (Leventhal et al., 2007; Weinberger, Smith, Kaufman, & McKee, 2014).

These results should be considered in conjunction with the null results from the other moderations analyses; that is, neither specific craving reduction expectancies nor dependence appeared to moderate any of the outcome measures. Such moderation would have bolstered the evidence of expectancy-driven effects on craving. Furthermore, e-cigarette dependence also failed to moderate effects observed in the study. As e-cigarette research is novel, measurement and conceptualization issues may be complicating the results of this study, in that e-cigarette dependence may not present in the same way as cigarette dependence. On a similar note, perhaps the nicotine dose used in this study was insufficient to produce drug effects on some outcome measures (Eissenberg, 2010), or the device used was not strong enough to deliver sufficient dose (Farsalinos et al., 2014). Blood nicotine levels would be required to verify nicotine delivery.

Psychological Reward and Enjoyment of Respiratory Tract Sensations

In contrast to hypotheses, there were no main effects observed for other outcome variables; however, significant interactions between drug content and instructional set were observed. The implications of the particular pattern of interactions require speculation, but can provide insight into the outcomes of e-cigarette use.

In terms of psychological reward, the True Positive condition had higher scores than the Placebo and Anti-Placebo conditions. This suggests that in order for an increase in perceived reward after vaping, stimulus expectations regarding nicotine content and actual drug dose should be present. Of note, the psychological reward factor of the modified mCEQ contains items related to relaxation, hunger and negative affect reduction, and increased stimulation and concentration. As outlined previously, both nicotine content and outcome expectancies can shape reactions within these domains (e.g. Brandon, Juliano, & Copeland, 1999); therefore, our results are consistent with previous tobacco research in that the interaction showed a significant effect.

An interaction was also observed in terms on the enjoyment of respiratory tract sensations. We had hypothesized that this outcome would be affected primarily by the nicotine dose manipulation. However, the effect was found when the instructional set and actual nicotine dose were congruent—i.e., in both the True Positive and True Negative conditions. As a potential explanation of these results, it should be considered that previous research suggests that the physical experience of vaping may be, in general, more enjoyable and less aversive than smoking (Harrell et al., 2015), and some preliminary research findings support this at a biological level (Tobacco Advisory Group of the Royal College of Physicians, 2016). However, the balanced-placebo design itself should also be considered. It has been postulated that effects elicited in the Placebo group and Anti-Placebo groups within balanced placebo designs are

difficult to interpret due to the drug dose (Perkins, Sayette, Conklin, & Caggiula, 2003). In terms of the Placebo conditions, individuals who use the drug daily are not accustomed to receiving a non-dose, which may generate a less enjoyable experience. Along the same lines, those in the Anti-Placebo condition may have received too large of a dose, especially when they expected the drug to be absent. Thus, the enjoyment of the e-cigarette used in the current study may have been affected by this incongruence of drug and stimulus expectancies.

Clinical Implications

The purpose of the present study was to provide an objective foundation in which to investigate the potential addictive liability of this emerging product. Perhaps one of the most clinically significant findings from this study is that urges to smoke were significantly reduced after use of an e-cigarette believed to contain nicotine, regardless of the nicotine content. This effect was particularly robust for males. Although the majority of smokers report using e-cigarettes to try to quit smoking, there have been limited clinical trials investigating the efficacy of this process. Results from the present study suggest causality: cigarette urge reduction may be due in part to an expectancy effect. Placebo effects appear to have emerged in prior clinical trials in that non-nicotine (placebo) e-cigarettes prompted smoking reduction or cessation. For example, in Bullen et al. (2013), results of the randomized clinical trial showed no differences in efficacy between e-cigarettes with and without nicotine, both of which performed just as well as nicotine patches. Another RCT (Caponnetto et al., 2013) found that cigarette use was reduced to the same degree among all participants who, as a part of the trial, received different doses of nicotine (including nicotine-free) e-cigarettes. The present study provides a potential mechanism for these observed effects. Results should be considered in conjunction with observations from our participant demographics, which suggested dual users are smoking fewer cigarettes than their

mono-product counterparts. Thus, evidence suggests that vaping reduces desire to smoke through expectancies rather than pharmacology alone, perhaps leading to reduction in smoking.

Higher reward and enjoyment of respiratory tract sensations resulted from the combination of nicotine content and matching expectations about the drug content. In conjunction with reductions in vaping cravings elicited through the combination of nicotine and congruent beliefs, these results provide further insight into the addictive potential of e-cigarettes. That is, expectancies and nicotine increase some positive effects of e-cigarette use. Reward, enjoyment of physical sensations, and craving reduction may promote the use of the drug and the development of salient expectancies. Altogether, this may lead to the maintenance of repeated drug administration, or create barriers to discontinuation of e-cigarette use.

Limitations

The results of this study should be considered within the context of several methodological issues. First, the null findings must be addressed. There was an interaction effect between nicotine and instructional set on satisfaction that did not reach significance. Effects may not have reached significance in the present study for a number of reasons; one being that the satisfaction factor in the modified mCEQ includes an item relating to taste. A large portion of participants in the sample reported use of other flavors, namely those falling into dessert/custard category. Within the outcome of sustained attention, main effects of both nicotine and expectancies approached significance in the hypothesized direction. As discussed later, it is possible that a higher nicotine dose might have produced a stronger effect. Finally, no trends in results from the main manipulation were found for mood, hunger, or aversion. It can be speculated that changes in mood and hunger may be less immediate than cravings, reward, and respiratory enjoyment. In terms of aversion, the findings from the present study somewhat

support previous research that shows e-cigarettes are thought to be less aversive than traditional cigarettes (Harrell et al., 2015).

In terms of the methodology, error variance may have been produced by elements related to variability in e-cigarette devices, solutions, and use patterns. There is a great deal of heterogeneity within products and e-cigarette use, and participant characteristics illustrate the natural variability of e-cigarette use; most reported using third-generation “mod” devices, a preference for flavors not offered in this experiment, and varied ranges in use patterns. The present study aimed to assess the addictive liability of e-cigarettes through a well-controlled experiment, and thus, at the cost of generalizability. However, a strength of this study is that a more preferred second-generation device was used, as previous research in this area has typically opted for the first-generation devices. Participants were not novice users either, another strength over previous research that increases generalizability. Another important methodological consideration is that participants were asked to come into the laboratory having abstained from cigarettes or e-cigarettes for 3 hours; thus, inducing a mild withdrawal state. Other states (such as mood or hunger) were not otherwise altered prior to the session, but could be induced in future research to provide a higher baseline upon which to test the effects of vaping.

Another consideration when interpreting findings from this study is that there were main effects upon post-vaping estimated nicotine dose of both instructional set and nicotine content. Thus, individuals could detect differences in nicotine level—at least in retrospect, when asked directly. This could be interpreted as a failure of the nicotine dosing blind, or simply that true nicotine effects were perceived, as suggested by outcome variables including desire to vape, psychological reward, and respiratory track enjoyment. Nevertheless, such detection complicates the interpretation of expectancy effects within the balanced-placebo design (Martin

& Sayette, 1993). Despite these limitations, as the first fully-crossed balanced-placebo experiment using e-cigarettes (to our knowledge), this study shows that this design can be feasibly implemented and produce valuable results.

Finally, limitations from the design of the experiment and the data analysis should be addressed. First, several of the measures (e.g., e-cigarette expectancy scales) used in this study were adapted from cigarette questionnaires, any they have not yet been validated for e-cigarettes, specifically. Thus, it is not known whether they adequately capture the intended constructs. Some scales were composed of a single-item (e.g. aversion on mCEQ), which limits the ability to assess internal-consistency reliability and potentially limits their validity. Finally, other measures that have previously shown good psychometric properties show poorer reliability in this sample, namely the dependence measures. Results from this study should be interpreted in light of these considerations. In addition, the number of statistical tests proposed and performed was certainly elevated, which could have inflated the Type I error rate. This being said, this was planned as an initial exploratory study of multiple potential acute effects of e-cigarette use. As the area of e-cigarette use is still developing in the literature, the risk for Type II error would have been more detrimental. On the same note, including this number of dependent variables could have potentially diluted the effects, as some of the experimental effects may have faded prior to the collection of all the dependent variables. The benefit of this study design is it can be considered a preliminary foundation for evaluating drug and expectancy effects on e-cigarette use. Future research could utilize these findings to design narrower, well-controlled experiments to further evaluate specific outcomes, such as craving reduction.

Conclusions

The present study utilized a balanced-placebo design to test experimentally the independent and synergistic effects of nicotine and expectancies on e-cigarette use outcomes. The clearest, and most clinically-relevant, finding was that desire to smoke decreased when participants were told that their e-cigarette contained nicotine, regardless of the actual nicotine content. However, subsequent analyses revealed that this effect occurred solely in males. These findings indicate that beneficial effects of vaping upon smoking behavior may be driven by non-pharmacological factors, such as outcome expectancies. Although the clinical utility of e-cigarettes for smoking cessation is still unsettled, these findings are informative regarding possible mechanisms of action, they may explain some early clinical findings (Bullen et al., 2013; Caponnetto et al., 2013), and they may be useful for guiding intervention and policy development. Future studies could expand upon this finding by investigating e-cigarette effects on different classes of cigarette cravings, including those provoked by nicotine-withdrawal (as in current study), cue-reactivity, and affective states, as well as further probing gender differences. Finally, this study demonstrated that a balanced-placebo design can be feasibly implemented with e-cigarettes to elicit observations about the nature of these products.

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