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The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers

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Abstract

Objective—Flavored e-cigarette use has risen rapidly, especially among young adults who also smoke cigarettes. We sought to determine whether flavoring enhances the subjective rewarding value, relative reinforcing value, and absolute reinforcing value of an e-cigarette with nicotine compared to an unflavored e-cigarette with nicotine.

Methods—Using a within-subjects design, young adult smokers (n=32) participated in three human laboratory sessions. Session 1 evaluated the rewarding value of flavoring by having participants rate unflavored and flavored e-cigarettes with nicotine. Session 2 assessed the relative reinforcing value of a flavored vs unflavored e-cigarette via a choice task that evaluated the willingness to “work” to hit targets on a computer screen to earn flavored or unflavored e-cigarette puffs. Session 3 measured the absolute reinforcing value of flavored versus unflavored e-cigarettes via a 90-minute ad-libitum vaping session where puffs from each e-cigarette were counted.

Results—Subjective reward value was higher for the flavored versus the unflavored e-cigarette ($\beta=.83$, CI 0.35 to 1.32, $p=0.001$). Participants worked harder for flavored e-cigarette puffs versus unflavored e-cigarette puffs (breakpoint = 5.7; 597 responses versus 127 responses; $\beta=460.733$, CI 246.58 to 674.88, $p<0.0001$). Participants took twice as many flavored puffs than unflavored e-cigarette puffs (40 vs 23 puffs; IRR=2.028, CI 1.183 to 3.475, $p=0.01$).

Conclusions—Flavoring enhances the rewarding and reinforcing value of e-cigarettes with nicotine, and thus their abuse liability in young adult smokers. Further research is necessary to

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Contributors

Dr. Audrain-McGovern conceived of the study, directed data collection, wrote the introduction, methods and discussion, oversaw analyses and the interpretation of the results, and edited the entire manuscript. Dr. Strasser aided in study conceptualization and provided feedback on drafts. Dr. Wileyto undertook the statistical analysis and wrote the results sections. All authors contributed to and have approved the final manuscript.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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determine whether the use of flavoring in e-cigarettes impacts cigarette smoking behavior among young adults.

Keywords

E-cigarettes; Flavoring; Young Adults; Smokers

1. INTRODUCTION

Electronic cigarette (e-cigarettes) use has risen rapidly, especially among young adults (14.2%) who also smoke combustible cigarettes (59.3%; Berg, 2016; Kalkhoran and Glantz, 2016; McMillen et al., 2015). The availability of flavoring is the most frequently reported reason young people give for initiating and continuing to use e-cigarettes (Pesko et al., 2016; Villanti et al., 2013). While this research highlights a preference for flavoring among young adults, the factors that underlie such preferences has yet to be investigated. Flavoring may increase the subjective rewarding value, the relative reinforcing value, and the absolute reinforcing value of e-cigarettes with nicotine compared to unflavored e-cigarettes with nicotine. We sought to examine these indices of abuse liability.

2. METHODS

2.1. Participants and Procedures

Young adult cigarette smokers were recruited from the community through print advertisements. Eligible smokers were between the ages of 18–30 years old, currently smoked > 5 cigarettes a day for at least one year, and had used an e-cigarette at least once. Smokers who had a carbon monoxide (CO) breath sample < 10 ppm, a positive urine screen for illicit drugs, psychotropic medication, or pregnancy were excluded. Smokers were also excluded from participation if they currently used nicotine products other than cigarettes, reported a psychiatric disorder (excluding nicotine dependence), and had never used an e-cigarette or used e-cigarettes daily. Young adult combustible cigarette smokers have the highest rate of e-cigarette use (Berg, 2016; Kalkhoran and Glantz, 2016; McMillen et al., 2015). We recruited a sample that was neither naïve to e-cigarettes nor regular consumers to elucidate how flavoring may underlie e-cigarette uptake in young adult smokers. This sampling approach was approved by the Institutional Review Board.

Individuals were prescreened for inclusion and exclusion criteria via telephone and those meeting initial criteria attended a screening visit. After providing written informed consent, potential participants provided a CO to verify smoking status and a urine sample for a drug screen and pregnancy test. E-cigarette use was quantified by asking “How many times in your lifetime (past month, past week) have you used an e-cigarette, e-hookah, vape pen or personal vaporizer?” Pictures of each of these were included to promote clarity. Participants received \$200 compensation for the completion of three laboratory visits. The second and third laboratory visits were separated by at least two days to allow smoking and nicotine intake to normalize after a 12-hour smoking abstinence period and a two-hour laboratory visit that prohibited smoking. Table 1 provides a summary of the sample characteristics (n=32).

2.1.1. Rewarding Value of E-cigarette Flavoring—At the initial visit, participants first received instructions for use and then had an opportunity to familiarize themselves with the tank-style e-cigarette by taking two puffs from a nonflavored e-cigarette without nicotine. The “e-GO” tank-style e-cigarette had a single 2.2–2.4 ohm resistance coil that could not be adjusted, 650 mAh rechargeable lithium ion battery and a 2.4 ml refillable e-liquid tank.

Participants then sampled three tank-style e-cigarettes; one contained unflavored e-liquid, one contained a fruit-flavored (green apple) e-liquid, and one contained a dessert-flavored e-liquid (chocolate). All three contained nicotine. The flavored and unflavored e-liquid was a 50/50 PG/VG blend containing 6, 12, or 18 mg/ml of nicotine depending on the nicotine content of the participant’s usual cigarette brand and their smoking rate. For example, if a participant reported smoking 15 cigarettes per day and their usual brand had .8 mg/cig (e.g., Marlboro Light, Newport 100s), we assigned that participant to receive a 12 mg/ml e-liquid (e.g., $.8 \times 15 = 12$). Of the 32 participants, 14 received the 6mg e-liquid, 12 received the 12mg e-liquid and 6 received the 18mg e-liquid. None of the participants reported that they found the e-cigarettes aversive.

Participants took two puffs from the nicotine alone e-cigarette, the fruit flavored e-cigarette, and the dessert flavored e-cigarette. We selected green apple and chocolate because sweet flavors are popular among e-cigarette users (Berg, 2016), promoting generalizability and the avoidance of exposure to aversive flavoring. The exposure to the three e-cigarettes was separated by 20 minutes each and the order of the three exposures was counterbalanced (Ray et al., 2006; Rukstalis et al., 2005). After each of the three e-cigarette exposures, participants completed measures of subjective reward.

2.1.2. Relative Reinforcing Value of E-cigarette Flavoring—For the second visit, participants arrived at the laboratory at 9:00 a.m. after overnight (12-hours) abstinence (CO-verified < 10 ppm). In preparation for the assessment of the relative reinforcing value of flavor (RRVF), participants received an introduction to a validated behavioral choice paradigm (Lussier et al., 2005; Perkins et al., 1994, 2009; Yoon et al., 2009) whereby they had the chance to earn points for flavored or unflavored e-cigarette puffs. The goal was to determine the motivation to use a flavored e-cigarette rather than to quantify the reinforcing value of specific flavors. The e-cigarette flavor with the highest rewarding value (measured at visit 1) served as the flavor for this assessment.

Assessment of the RRVF was accomplished by asking the participants to perform work, in the form of moving a computer mouse to hit targets on one of two computer screens, to earn points toward flavored or unflavored e-cigarette puffs. Using a concurrent schedule (Audrain-McGovern et al., 2015, 2014; Perkins et al., 1994; Perkins et al., 2002), participants were told that they could switch from working on one screen to the other as often as they wished. Participants were instructed to move the computer mouse to have the cursor hit the targets (either an apple/piece of chocolate or a water droplet alongside an e-cigarette; Norman and Jongerius 1985; Perkins, 2009; Perkins et al., 1994). Consistent with relative reinforcement paradigms, the reinforcement schedule in the unflavored e-cigarette earning screen remained constant at a fixed ratio FR-25 (25 targets achieved to earn a point) while the reinforcement schedule for the flavored e-cigarette increased (required more

effort) with a progressive ratio schedule of PR-25x over 10 trials, such that 25, 50, 75, 100, 125, 150, 175, 200, 225, and 250 targets had to be achieved to earn a point (Audrain-McGovern et al., 2015, 2014; Bickel et al., 2000; Epstein et al., 2007). As such, this task determined how reinforcing flavored puffs were relative to unflavored puffs by the willingness of the participant to work increasingly harder for them. RRVF was defined by the breakpoint or the highest trial (out of 10 trials) that was completed for flavored e-cigarette puffs.

The computer task was performed until a participant completed 10 trials and accumulated a total of 10 points from which they earned either one puff of an unflavored e-cigarette for each point (i.e., up to 10 puffs of an unflavored e-cigarette) or one puff of a flavored e-cigarette for each point (i.e., up to 10 puffs of a flavored e-cigarette). E-cigarette puffs were taken at the end of the procedure to prevent satiation from influencing responding in subsequent trials. To ensure that responding in the choice task was based on reinforcer preference rather than departure from the laboratory, the choice task was followed by a 1-hour wait in the laboratory.

2.1.3. Absolute Reinforcing Value of E-cigarette Flavoring—For the third visit, participants arrived at the laboratory at 9:00 a.m. after overnight (12-hours) abstinence (CO-verified < 10 ppm). The absolute reinforcing value of flavored e-cigarettes as measured by a 90-minute ad libitum vaping paradigm in the laboratory, provided a measure of overall consumption (Arnold and Roberts, 1997). At this visit, participants had the opportunity to self-administer the unflavored or the flavored e-cigarette that the participant sampled at visit 1 and chose for the RRVF task at visit 2.

Participants were taken to a specially ventilated and approved smoking research room equipped with a sofa, a table and a television monitor. Participants were told that they would have a 90-minute laboratory waiting session where they would periodically complete questionnaires while they waited. Participants were told that the 90-minute laboratory session would be followed by a 30-minute period of enforced abstinence from vaping and smoking (Mueller et al., 2009). The labeled e-cigarettes were placed on a table next to the couch. Participants were observed via an observation window by a research assistant who monitored and counted the number of e-cigarette puffs taken (from each of the two e-cigarettes) during the 90-minute period (Audrain-McGovern et al., 2015; Cousins et al., 2001; Mueller et al., 2009). The ad-lib session was videotaped to independently score the number of puffs taken.

2.2. Measures

2.2.1. Covariates—Standard survey questions were used to collect demographics, combustible cigarette smoking history and e-cigarette use history. The Fagerstrom Test for Nicotine Dependence (FTND) was administered to assess nicotine dependence (Heatherton et al., 1991).

2.2.2. Outcome Variables—The subjective rewarding value of e-cigarette flavoring was measured with the Satisfaction subscale of the Cigarette Evaluation Scale (CES) adapted for e-cigarette use (Ray et al., 2006; Rukstalis et al., 2005; Westman et al., 1992). The Likert-

format responses (1=not at all to 7=extremely) to the two Satisfaction subscale items (“Was it satisfying?” and “Did it taste good?”) were averaged.

RRVF was measured with a validated choice task, evaluating the motivation to “work for” flavored versus unflavored e-cigarettes (Lussier et al., 2005; Perkins et al., 1994; Yoon et al., 2009). It was defined by the breakpoint or the highest trial that a participant successfully worked for a flavored puff. Higher values reflected greater reinforcing value of flavored relative to unflavored e-cigarettes (Bickel et al., 2000; Epstein et al., 2007). We included the total number of responses for the flavored versus the unflavored e-cigarette as a secondary RRVF outcome. The absolute reinforcing value of e-cigarette flavoring was operationalized as the number of flavored versus unflavored e-cigarette puffs consumed during the ad libitum vaping session (Cousins et al., 2001; Mueller et al., 2009).

3. RESULTS

3.1. Descriptive and Bivariate Statistics

All analyses were conducted within Stata (Stata Corporation, College Station, TX, USA). The average subjective rewarding value across the three e-cigarettes included: unflavored ($M = 3.11$, $SD = 1.55$), dessert flavored ($M = 3.69$, $SD = 1.78$), and fruit flavored ($M = 4.22$, $SD = 1.55$). Both the fruit flavored ($\beta = 1.11$, $CI\ 0.58\ to\ 1.64$, $p < 0.0001$) and the dessert flavored e-cigarettes ($\beta = .57$, $CI\ 0.47\ to\ 1.11$, $p = 0.03$) were rated significantly more rewarding than the unflavored e-cigarette, while the fruit flavoring was preferred to the dessert flavoring ($p = .05$). The RRVF task revealed an average breakpoint of 5.7 ($SD = 3.6$), indicating that the participants were willing to work harder to earn puffs from a flavored than the unflavored e-cigarette; typically shifting to work for unflavored puffs at trial six. Total work was 596.31 responses (mouse clicks on targets) for the flavored e-cigarette ($SD = 520.25$; Range 0 – 1,375) and 126.66 for the unflavored e-cigarette ($t(31) = 4.37$, $p = .0001$; $SD\ 90.31$; Range 0 – 250). The absolute reinforcing value of flavoring assessment showed that participants took an average 40.29 puffs ($SD = 30.86$; Range 1 – 113) from the flavored e-cigarette and 23.22 puffs ($SD = 33.85$; Range 0–147) from the unflavored e-cigarette during the 90-minute ad-libitum vaping session (40 vs 23; $t(30) = 2.30$, $p = .02$).

3.2. Multivariate Models

Regression models were used to evaluate the effect of flavor (averaged values for fruit and dessert with unflavored as reference) on the outcomes while controlling for the effects of sex, regular menthol cigarette smoking, nicotine dependence, and lifetime e-cigarette use (Table 2). However, flavor is inherent in the breakpoint outcome and was not included as a predictor in this linear regression. Bonferroni correction for three primary outcomes meant that the threshold for significance was $p = 0.0167$. The total number of responses for the flavored versus the unflavored e-cigarette was included as a secondary RRVF outcome, because it includes all responding, not just that associated with successful trial completion.

Subjective reward was higher for the flavored e-cigarette compared to unflavored ($\beta = .83$, $CI\ 0.35\ to\ 1.32$, $p = 0.001$). This group difference meant that participants rated the unflavored e-cigarettes as “a little” and the flavored e-cigarette as “moderately” satisfying and good

tasting. Participants took twice as many flavored puffs than unflavored e-cigarette puffs (IRR=2.028, CI 1.183 to 3.475, $p=0.01$). Menthol cigarette smokers took over three times as many e-cigarette puffs as non-menthol smokers (IRR=3.21, CI 1.69 to 6.08, $p=0.0001$). None of the covariates were significant in the models for breakpoint or the total number of responses for flavored versus unflavored e-cigarettes. Consistent with a breakpoint of 5.7, participants responded on average 126 times for unflavored puffs, but almost 597 times toward flavored puffs ($\beta=460.733$, CI 246.58 to 674.88, $p=0.00002$).

4. DISCUSSION

These data offer new evidence that flavoring enhances the rewarding and reinforcing value of e-cigarettes with nicotine, and thus their abuse liability in young adult smokers. Young adult cigarette smokers have the highest rate of e-cigarette use (Berg, 2016; Kalkhoran and Glantz, 2016; McMillen et al., 2015). Flavoring may underlie e-cigarette uptake in this population, fostering the dual use of e-cigarettes and combustible cigarettes. Young adult smokers reported that they liked (more satisfying, better taste) the flavored e-cigarettes more than the unflavored e-cigarette. In addition, they were willing to work almost six times as hard for the opportunity to take flavored e-cigarette puffs in a behavioral choice task. The significance of their choices is highlighted by the fact that the participants were abstinent from cigarette smoking for 12 hours and an unflavored e-cigarette with the same amount of nicotine was concurrently available at a lower behavioral cost (10 puffs for 250 responses versus 10 puffs for 1,375 responses). The higher hedonic and relative reinforcing value of flavoring translated to almost double the consumption of a flavored versus an unflavored e-cigarette under ad-libitum vaping conditions.

These findings raise several important questions about e-cigarette use and cigarette smoking among young adults. First, is flavoring in e-cigarettes with nicotine sufficiently rewarding and reinforcing to allow e-cigarettes to substitute for combustible cigarettes? The enhanced appeal, rewarding value and reinforcing value of e-cigarette flavoring may facilitate e-cigarette use and may aid in the reduction or cessation of combustible cigarettes, lessening exposure to known toxins in combustible cigarettes (Cahn and Siegel, 2011; Goniewicz et al., 2014). Investigation of the reinforcing efficacy of flavored e-cigarettes relative to combustible cigarettes would help provide important answers to this question. Likewise, definitive data supporting the efficacy of e-cigarettes for smoking reduction or smoking cessation are absent (Grana et al., 2014; Kalkhoran and Glantz, 2016; Vickers et al., 2013) highlighting the need for further research.

Second, does flavoring enhance the rewarding and reinforcing value of e-cigarettes with nicotine such that young adult smokers continue to use both e-cigarettes and combustible cigarettes? Cross-sectional surveys indicate that up to half of smokers who use e-cigarettes do not smoke fewer combustible cigarettes (Rass et al., 2015; Rutten et al., 2015). Flavoring may foster the use of e-cigarettes among young adult smokers, increase nicotine exposure, and result in higher levels of nicotine dependence. Young adults also may learn that e-cigarettes can be used in place of combustible cigarettes in nonsmoking situations (Rass et al., 2015), minimizing the inconvenience of being a smoker, and diminishing motivation to quit smoking. It will be important to translate our laboratory findings of vaping behavior to

population-level studies by determining the impact that flavoring has on e-cigarette use, combustible cigarette smoking and nicotine dependence trajectories in young adults.

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Highlights

- Flavoring enhances the rewarding and reinforcing value of e-cigarettes with nicotine.
- Flavoring may increase the abuse liability of e-cigarettes with nicotine in smokers.
- The absence of flavoring in e-cigarettes with nicotine may result in decreased use.

Table 1

Sample Characteristics (N=32)

Demographics	
Sex	–
Female, <i>n</i> (%)	12 (38.0)
Male, <i>n</i> (%)	20 (62.0)
Age, <i>M</i> (SD)	25.0 (3.0)
Race/Ethnicity, <i>n</i> (%)	–
Asian	2 (6.0)
Black/African American	14 (44.0)
White	14 (44.0)
Multi-ethnic/Multi-Racial	2 (6.0)
Hispanic Ethnicity, <i>n</i> (%)	5 (16.0)
Highest education, <i>n</i> (%)	–
Some high school	1 (3.0)
High school graduate	7 (22.0)
Some college	17 (53.0)
College graduate	7 (22.0)
Smoking/E-cigarette History	
Cigs per day, <i>M</i> (SD)	11.4 (8.7)
Menthol Smoker, <i>n</i> (%)	18 (56.2)
Nicotine Dependence, <i>M</i> (SD)	3.66 (2.5)
Lifetime E-cig Use, <i>M</i> (SD)	12.0 (15.4)

Note. Lifetime e-cigarette use was the number of times (episodes) that an e-cigarette was used.

Table 2**Regression Models Adjusted for Covariates**

Predictor	Subjective Rewarding Value			Outcome			Absolute Reinforcing Value		
	β	Confidence Interval	p value	β	Confidence Interval	p value	IRR	Confidence Interval	p value
Flavored	.83	.35, 1.32	.001	–	–	–	2.03	1.18, 3.47	.01
Sex	.41	–.56, 1.38	.41	2.31	–.64, 5.28	.12	.99	.61, 1.65	.99
Menthol	.69	–.41, 1.79	.22	–.01	–.01, .01	.60	3.21	1.69, 6.08	<.0001
FTND	–.07	–.28, .15	.54	.19	–.49, .89	.57	.98	.87, 1.11	.79
E-cig Use	–.01	–.04, .03	.73	.39	–.12, .91	.13	1.01	.99, 1.02	.25

Note. FTND is the Fagerstrom Test for Nicotine Dependence. Sex is modeled for female. Menthol is modeled for menthol cigarette smoker.