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E-Cigarette Palatability in Smokers as a Function of Flavorings, Nicotine Content and Propylthiouracil (PROP) Taster phenotype

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Abstract

Background: The popularity of E-cigarettes is due in part to their flavorings. The purpose of this study was to determine the effect on smokers' sensory perceptions and liking of various e-cigarette flavorings, and the degree to which those perceptions are influenced by nicotine level, sex, and PROP bitter taster phenotype.

Methods: We recruited 132 non-treatment-seeking, daily cigarette smokers. In repeated trials in one laboratory session participants vaped the Joyetech eGo-C e-cigarette with each of the following flavorings (in random order): unflavored, tobacco, cherry, chocolate, and menthol. Participants vaped the e-juice first without nicotine and then with high nicotine (18mg/ml), and provided sensory (bitterness/sourness, irritation, sweetness) and liking ratings. Perceived intensity of 6-n-propylthiouracil (PROP) was used to classify the participants as non-tasters (n=28), medium-tasters (n=74), or supertasters (n=28). Mixed-effects linear models and generalized estimating equations were used to evaluate ratings as a function of flavor interacting with nicotine content, sex and taster phenotype, adjusting for age, race/ethnicity, menthol use, and nicotine dependence.

Results: Regardless of nicotine level, cherry ($\beta=1.76$, $p<0.001$) and chocolate ($\beta=0.69$, $p<0.001$) were rated as sweeter, but were not better liked, than unflavored e-juice. Menthol elicited the

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Contributors

MDL and CO conceptualized the study and selected the measures. MDL wrote the grant application that outlined its design, with assistance from VD. MDL and VD wrote the procedure manuals. MDL supervised the overall project, and VD supervised those aspects related to taste and smell testing. MDL and ELM designed and implemented the data analysis. ELM wrote the primary draft of the manuscript and edited all subsequent drafts. MDL, VD and CO provided critical interpretation of the results and edited the manuscript. All authors approved the final manuscript.

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Conflict of Interest

All authors declare that they have no conflicts of interest.

highest liking rating, especially for women ($\beta=12.23$, $p<0.05$) and supertasters ($\beta=20.52$, $p<0.05$). Regardless of flavor, high nicotine was rated as more irritating (OR=1.43, 95% CI=1.02–2.01) than the no-nicotine e-juice. Irritation ($\beta= -13.65$, $p<0.001$), bitterness/sourness ($\beta= -11.38$, $p<0.001$), and sweetness ($\beta=4.79$, $p<0.001$) were associated with liking.

Conclusion: Menthol may enhance e-cigarette palatability for some smokers, which may increase e-cigarette utility in smoking cessation.

Keywords

E-Cigarettes; Flavoring Agents; Nicotine; Smokers; Sex Factors; Taste Perception

1. Introduction

The use of electronic nicotine delivery systems (e-cigarettes) has rapidly increased (King, Patel, Nguyen, & Dube, 2015; McMillen, Gottlieb, Shaefer, Winickoff, & Klein, 2015; Regan, Promoff, Dube, & Arrazola, 2013), even as overall smoking has declined (Jamal et al., 2015). According to the Population Assessment of Tobacco and Health study, 5.5% of U.S. adults currently use e-cigarettes (Coleman et al., 2017; Kasza et al., 2017). E-cigarettes are a diverse group of products in which a battery-powered heating element heats a propylene glycol- or glycerine-based liquid (commonly referred to as e-juice) into an aerosol for users to inhale. E-cigarette juices typically contain nicotine and a flavor additive. The aerosol may be less harmful than combustible smoke, and substituting e-cigarettes could improve smokers' health (Goniewicz et al., 2014; Levy et al., 2018; McAuley, Hopke, Zhao, & Babaian, 2012; National Academies of Sciences Engineering and Medicine, 2018).

E-cigarette users often report that these products help them quit smoking and/or improve their health (Berg, 2016; Coleman et al., 2017; Etter, 2010; Foulds, Veldheer, & Berg, 2011). For established smokers seeking to quit or to reduce their use of cigarettes, e-cigarettes have shown some benefit, especially those containing nicotine (Masiero et al., 2018; National Academies of Sciences Engineering and Medicine, 2018; Rahman, Hann, Wilson, Mnatzaganian, & Worrall-Carter, 2015; Tseng et al., 2016). However, 70% of e-cigarette users also smoke cigarettes (Coleman et al., 2017; Kasza et al., 2017), thus mitigating their potential benefits. The degree to which smokers may switch to an e-cigarette may depend in part on its palatability, i.e., the degree to which e-cigarettes are liked.

Manufacturers use flavorings to enhance e-cigarette appeal and palatability. By a recent estimate, e-cigarettes had over 7,700 customizable flavorings available (Zhu et al., 2014). Users report flavorings as a significant reason for e-cigarette initiation and current use, and approximately two-thirds of users use non-tobacco flavorings (Berg, 2016; Coleman et al., 2017; Villanti et al., 2017). The most popular are sweet (e.g., fruit, dessert) and menthol/mint flavorings (Berg, 2016; Giovenco, Hammond, Corey, Ambrose, & Delnevo, 2015). Fruit flavors are most popular among former and never-smokers, whereas menthol/mint is most popular among current smokers (Bonhomme et al., 2016). Flavorings can reduce the harsh taste of tobacco, resulting in increased inhalation, enhanced nicotine delivery, and increased product attractiveness (Carpenter, Wayne, Pauly, Koh, & Connolly, 2005; Klein et al., 2008; Kostygina, Glantz, & Ling, 2016; Rabinoff, Caskey, Rissling, & Park, 2007;

Squier, Mantz, & Wertz, 2010; Sterling, Fryer, Nix, & Fagan, 2015). Flavored e-cigarettes may help smokers reduce or quit smoking (Buu, Hu, Piper, & Lin, 2018; Chen, 2018; Tackett et al., 2015).

Nicotine has a bitter and irritating taste, and flavoring may help mask it (Arendt Nielsen, Nielsen, Wang, Arendt-Nielsen, & Boudreau, 2016; Dessirier, O'Mahony, & Carstens, 2001; Fan et al., 2016). However, to date this effect has not been explored with e-cigarettes. Flavor is perceived through a complex system of tastes (sweet, sour, salty, umami, bitterness), smell pathways through the mouth and nostrils, and somatosensory experiences (touch, temperature, pain) (Duffy, Hayes, Bartoshuk, & Snyder, 2017; Shepherd, 2006). Individuals vary in perception of flavor, and one marker for this variation is the ability to taste the bitterness of propylthiouracil (PROP). "Supertasters" of PROP (those with heightened oral sensations) and women (who are more likely to be PROP supertasters) may be more susceptible to the bitternessmasking effects of flavorings in e-cigarettes (Bartoshuk, Duffy, & Miller, 1994; Mojet, ChristHazelhof, & Heidema, 2001). Individual differences in oral sensation might affect the uptake of e-cigarette use, but this possibility has received limited attention in the literature.

The present study examined the effects of altering nicotine concentrations and flavorings in e-cigarettes on pleasant (sweet) and unpleasant (bitter/sour, irritating) oral sensations and liking among non-treatment-seeking cigarette smokers. This group was used because they represent a target population: those who smoke who may switch to e-cigarettes. We expected that flavored e-juice would be perceived with more pleasant/less unpleasant sensations and be more liked than unflavored e-juice. Furthermore, we expected that high nicotine e-juice would be perceived with more unpleasant/ less pleasant sensations, but more liked than no-nicotine e-juice, due to the activating and rewarding effects of nicotine. We also sought to determine whether flavor and nicotine preferences were moderated by sex and by PROP bitter taster phenotype. The results could have implications both for the regulation of flavors in e-cigarettes, and for the use of e-cigarettes in smoking cessation efforts.

2. Materials and methods

This report presents the findings from the laboratory phase (Phase I) of a two-phase study (Litt, Duffy, & Oncken, 2016) that examined the effects of e-cigarette flavors and nicotine levels on smoking and e-cigarette use in current cigarette smokers. In this phase participants were administered measures of smoking history, and taste and smell history, and then participated in laboratory-based sensory testing. In this testing smokers reported the pleasant and unpleasant sensations from, and their liking of, e-cigarettes with e-juices of various flavorings, and with no- and high-nicotine concentrations. All Phase I procedures were completed in one visit at baseline. Details regarding Phase II of the study can be found in Litt et al. (2016). The Institutional Review Board of the University of Connecticut Health Center approved the study. Participants provided written informed consent and were paid for participation.

2.1 Participants

We recruited men and women smokers, ages 18–45 years, who currently smoked 10 cigarettes daily, and were willing to abstain from cigarette smoking and substitute e-cigarettes for six weeks (required for Phase II of the study), not planning to stop smoking (scored < 2 on Intentions to Quit scale), and able to read and understand English. Individuals with the following conditions were excluded: unstable medical or psychiatric disorders (including hypertension) as determined by a physician, current or planned pregnancy, known hypersensitivity to nicotine or propylene glycol, previous myocardial infarction or stroke, insulin dependent diabetes, or known chronic obstructive pulmonary disease or asthma. Individuals who had used e-cigarettes on more than two occasions were excluded. Participants were recruited from the greater Hartford, CT area using newspaper and radio advertisements from March 2015 – March 2016.

The sample included 132 adults (65 men, 67 women), had a mean age of 37.8 years ($SD=10.4$), and were 68% non-Hispanic (NH) white, 23% NH black, and 9% other or multiracial. About 62% preferred menthol cigarettes. The average Fagerström Test for Cigarette Dependence (FTCD) score was 5.4 ($SD=2.0$) (moderately high level of dependence). Participants were regular daily smokers for an average of 19.0 years ($SD=10.8$), and smoked an average of 25.1 ($SD=9.4$) cigarettes/day. Participants were asked not to smoke for at least three hours prior to the visit, and not to consume any substance that might impair taste (such as coffee) the morning of the testing. The mean exhaled carbon monoxide (CO) level was 15.83 ppm ($SD=8.86$, Range=10–41), indicating that, on average, they had smoked within the past eight hours (Sandberg, Sköld, Grunewald, Eklund, & Wheelock, 2011).

2.2 Measures

2.2.1 Demographic and Smoking Characteristics—Participants completed a demographic survey that captured age, sex, and race/ethnicity. The Smoking History Questionnaire (SHQ), a self-report survey of smoking history and patterns, was administered (Brown, Lejuez, Kahler, & Strong, 2002). Participants indicated their preference for menthol versus non-menthol cigarettes, and completed the FTCD, which was scored from 0–10 (Fagerström, 2012; Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

2.2.2 PROP Testing to Define Bitter Taster phenotype—Participants received training on using the general Labeled Magnitude Scale (gLMS) to rate sensory intensity, following the National Health and Nutrition Examination Survey (NHANES) protocol (https://wwwn.cdc.gov/Nchs/Nhanes/2013–2014/CSX_H.htm). The relative bitterness of concentrated PROP to saltiness of sodium chloride in sampled aqueous solutions was used for bitter taster phenotyping (Bartoshuk et al., 1994; Mojet et al., 2001). Room temperature tastants were delivered in 10 ml amounts. After sipping, sampling and expectorating, participants rated each tastant intensity on the gLMS with end-points of “barely detectable” (1.4) and “strongest sensation of any kind” (100), and intermediate anchors (weak (6), moderate (17), strong (34.7), and very strong (52.5)) placed at log-scaled intervals (Bartoshuk et al., 2004). We characterized 28 non-tasters, 74 medium-tasters, and 28

supertasters. Taster phenotype did not differ between men and women ($\chi^2(2)=3.07$, $p=0.215$).

2.2.3 Ratings of Flavor Attributes—After sampling each e-juice by vaping, participants rated the bitterness/sourness, irritation, and sweetness using the gLMS. Participants also rated the level of liking/disliking on the hedonic gLMS (± 100 as strongest liking/disliking, 0 as neither like nor dislike and intermediate labels as above).

2.3 Procedure

After smoking history and demographic surveys, participants completed the taster phenotyping (see 2.2.2). Next, they were introduced to the Joyetech eGo-C (Shenzhen Joyetech), which was chosen because of its durability and flexibility regarding choice of base vehicle and size of atomizer reservoirs. The e-juice was purchased from Americaneliquidstore.com with a base of 50% vegetable glycerine – 50% propylene glycol and the following flavors: tobacco, chocolate, cherry, and menthol. These flavors were chosen for their popularity in smoking products (tobacco, menthol) and e-juices (chocolate, fruit). Nicotine concentrations tested were 0 vs. 18mg/ml, which is perceived by smokers as moderate to high (Etter, 2010; Foulds et al., 2011).

To familiarize participants with procedures they first vaped the unflavored, no-nicotine e-cigarette (base only) ad libitum for three minutes and rated the intensity of bitterness/sourness, irritation, sweetness, and liking. Participants then vaped e-juice with each flavoring (unflavored, tobacco, cherry, chocolate, and menthol, presented in random order) for one-minute without nicotine, and rated the sensations and liking, with a five-minute interval between each trial. Next, participants repeated these procedures with the same flavors and the same order, but with 18mg/ml of nicotine e-juice.

2.4 Data Analysis—The dependent variables were the sensory perception and liking ratings of the e-juices. Bitter/sour and irritation ratings were not normally distributed and could not be normalized through any transformation. Between 26–40% recorded no sensation ratings. Therefore, bitter/sour and irritation were dichotomized into none vs. any intensity. Sweetness ratings were square root transformed to normalize their distribution. Liking ratings were normally distributed.

The independent variables were flavoring (unflavored, tobacco, cherry, chocolate, menthol), and nicotine concentration (none, high). The following covariates were entered: demographic characteristics (age, sex, race/ethnicity), menthol smoking preference, and FTCD score. We explored years of daily smoking and cigarettes per day as covariates. However, Wald χ^2 tests indicated that they were not significant predictors of sensory perceptions and were subsequently dropped.

Generalized estimating equations (GEE) were used to evaluate bitterness/sourness and irritation as a function of the within-subject factors of flavoring, nicotine level, and menthol status, with demographics and FTCD as covariates (Zeger, Liang, & Albert, 1988). Variance inflation factors showed low collinearity between predictors. Mixed-effects linear regressions with restricted maximum likelihood estimation were used to evaluate sweetness

and liking ratings as a function of the same independent variables and covariates. All models treated participants as a random effect.

To determine if sensory ratings differed specifically by flavoring, nicotine content, sex, and taster phenotype, separate models were run employing different interaction terms as predictors: sex X flavor, sex X nicotine, taster phenotype X flavor, and taster phenotype X nicotine.

Because palatability is largely determined by liking, a final mixed model examined liking as a function of sensations (bitter/sour, irritation, sweet (transformed)), flavoring, nicotine content, taster phenotype, age, race/ethnicity, menthol smoking preference, and FTCD. Statistically significant interaction terms from previous models were also included. All analyses were conducted using SAS (version 9.4, SAS Institute, Cary, N.C., USA).

3. Results

3.1 Sensation and Liking by Flavor and Nicotine Content

Table 1 presents sensory and liking ratings by flavor and nicotine content averaged over all trials and all subjects. There was variability in the ratings. Tobacco flavor was rated as the most bitter/sour and irritating, regardless of nicotine content. Unsurprisingly, chocolate and cherry flavors were rated the sweetest. Interestingly, menthol was rated the most liked, regardless of nicotine content, whereas the chocolate flavored e-juice was rated the least liked, particularly with no nicotine. Regardless of flavoring, average bitterness/sourness, irritation, and sweetness ratings were similar regardless of nicotine content of the e-juice. High nicotine e-juices were rated as only slightly more liked than no-nicotine e-juice (mean = 14.32 vs. 11.76; $F_{(1,1287)}=1.76$).

3.2 Multilevel Models of Sensation and Liking as a Function of Flavor and Nicotine

Table 2 presents a summary of the results of the mixed effects analyses of sensory and liking ratings and their associations with flavorings and nicotine content. When adjusting for nicotine content, age, sex, race/ethnicity, menthol status, and FTCD, both sweetness and liking were influenced by e-juice flavorings. Participants rated cherry ($\beta=1.76$, $SE=0.19$, $p<0.001$) and chocolate ($\beta=0.69$, $SE=0.19$, $p<0.001$) flavorings as significantly sweeter than unflavored e-juice. Participants reported greater liking of menthol than unflavored e-juice ($\beta=9.39$, $SE=3.85$, $p<0.05$). Flavor was a significant predictor in the model of bitterness/sourness, but the GEE parameter estimates did not show any one flavor as statistically significantly different from unflavored e-juice. Ratings of irritation were not predicted by flavorings.

Adjusting for flavoring and baseline characteristics, irritation was predicted by nicotine content. Compared to no-nicotine e-juice, e-juices with high nicotine content were rated as more irritating (OR=1.43, 95% CI=1.02–2.01, $p<0.05$). Nicotine content was a significant predictor in the model of sweetness, such that high nicotine was rated as sweeter. Nicotine content was not associated with bitterness/sourness or liking. Additionally, the interaction term for flavor and nicotine content was not statistically significant, indicating that the sensory and liking ratings of individual flavorings did not differ by nicotine content.

Ratings of bitter/sour were predicted by sex, such that women had lower odds of rating e-juices as bitter or sour than men ($\chi^2=7.23$, $OR=0.48$; 95% $CI=0.28-0.81$, $p<0.01$). Overall liking of e-juices was higher among NH black than NH white participants ($F=5.31$, $\beta=14.07$, $SE=4.31$, $p<0.01$). Ratings of sweetness of e-juices were also predicted by race/ethnicity, but the mixed model parameter estimates did not show a significant difference between racial/ethnic groups.

3.3 Participant Sex and Taster phenotype as Moderators of Sensation and Liking

Table 3 presents a summary of the results of the hypothesized moderators: sex and taster phenotype interacting with flavoring and nicotine content. Overall, only one statistically significant interaction effect was found. Taster phenotype modified the flavor and liking relationship ($F=2.66$, $p<0.01$). Supertasters reported greater liking for menthol ($\beta=20.52$, $SE=8.25$, $p<0.05$) than for unflavored e-juice, adjusting for nicotine content, age, sex, race/ethnicity, menthol status, and FTCD. There were no effects among non-tasters and medium tasters. Figure 1 shows the results of the interaction.

Although the interaction term for flavor and sex was not a statistically significant predictor for Liking, mixed model parameter estimates showed that women rated menthol e-juice higher on Liking than unflavored e-juice ($\beta=12.23$, $SE=5.50$, $p<0.05$), but there was no difference among men.

3.4 Modeling Palatability: Liking as a Function of Sensations

The final mixed effects model examined liking and its association with bitter/sour, irritation, and sweet sensations, flavor, nicotine content, and baseline characteristics (age, sex, taster phenotype, race/ethnicity, menthol smoking status, and FTCD). Additionally, interaction terms for flavor X taster phenotype and flavor X sex were included because of their statistically significant associations in previous models (see section 3.3 above). Table 4 presents the results. Sweetness, irritation and bitterness/sourness were significant predictors of liking. E-liquids that were rated as irritating ($\beta=-13.65$, $SE=2.21$, $p<0.001$) or bitter/sour ($\beta=-11.38$, $SE=2.20$, $p<0.001$) were less liked than e-liquids rated as not irritating or bitter/sour. E-liquids that were rated as sweeter were better liked than those rated as less sweet ($\beta=4.79$, $SE=0.50$, $p<0.001$). A main effect for flavoring on liking emerged in this model, but no individual flavoring was most liked. A significant taster phenotype X flavor interaction modified this association ($F=2.92$, $p<0.01$). Supertasters reported higher preference for menthol flavoring than for unflavored e-juice ($\beta=17.89$, $SE=7.77$, $p<0.05$).

4. Discussion

Despite the popularity of flavored e-cigarettes, few studies have examined smokers' perceptions of the taste of flavorings and their level of liking. This information is necessary to better understand the use of flavors by e-cigarette users as well as the utility of flavored e-cigarettes for smoking cessation efforts. In the present study we sought to examine taste sensations and liking of potentially sweet and masking flavors, with no- vs. high nicotine content, of e-cigarettes in daily cigarette smokers with no intention of quitting and with no e-cigarette experience. We also focused on two groups who might be particularly responsive to

flavorings: women and those with heightened genetic ability to taste bitterness of PROP (supertasters).

We found some significant differences by flavorings in ratings of taste and liking. Contrary to expectations, we did not find any difference in bitterness/sourness or irritation by flavoring. Cherry and chocolate were rated as the sweetest, but were not better liked than unflavored e-juice. In contrast, menthol flavoring was the most liked, but this effect did not hold. After adjusting for sensations (e.g., irritation), the association between menthol and liking was non-significant, suggesting that sensations like irritation fully mediated this relationship. This is consistent with the finding that the preference for menthol may be due to its sensation of coolness (Kim et al., 2016; Rosbrook & Green, 2016).

Irritation had the largest effect on liking, followed by bitterness/sourness, demonstrating the importance of these oral sensations in the palatability of e-cigarettes for smokers. Both irritation and bitter/sour taste were inversely associated with liking, whereas sweetness had a smaller, but positive, association. Kim et al. (2016) reported similar findings in a sample of exclusive and dual e-cigarette users. Our findings suggest that the use of flavors to reduce bitterness/sourness and irritation could be more important than increasing sweetness to enhance e-cigarette palatability to smokers. There is, however, some perceptual confusion between smell and taste in e-cigarettes particularly with respect to the contribution of sweetness to liking (Rosbrook et al., 2017). In the present study, we did not have participants sample the e-cigarette with the nose plugged and unplugged to help focus attention on the retronasal perception of the e-juice flavor and the level of liking. Participants could have attributed a judgment of liking based on the flavor of the e-cigarette without regard to sweetness.

We had expected that flavorings would modify the sensory perceptions and liking of high nicotine content e-juice. Although high-nicotine was rated as more irritating than no-nicotine e-juice, this effect did not differ by flavor. This finding was surprising given evidence of the use of menthol and other flavorings in cigarettes to mask the irritation and harshness of smoking, and to enhance its chemosensory effects (Cummings, Morley, Horan, Steger, & Leavell, 2002; Kreslake, Wayne, Alpert, Koh, & Connolly, 2008; Kreslake & Yeger, 2010; Wayne & Connolly, 2002). The concentration of flavoring in the e-cigarette juice used in this study may partially explain the lack of masking effect. Studies have shown large variations in the concentrations of flavoring chemicals in e-liquids, even within the same type of flavor (Allen et al., 2016; Tierney, Karpinski, Brown, Luo, & Pankow, 2016). The level of masking depends on the concentration of flavor, the quality of the flavor (e.g., sweet, cooling) and the level of nicotine (Rosbrook & Green, 2016). Detailed chemical and sensory analyses are needed to determine if a high concentration of chemical flavorings can reduce the harshness of a high concentration of nicotine in e-liquids. Also, surprisingly, high-nicotine was not better liked than no-nicotine e-juice. This result might be due to lower than expected levels of nicotine delivery because of the type of device used (Farsalinos et al., 2014) or the amount of free-base form nicotine in the e-liquid (Duell, Pankow, & Peyton, 2018), or to individual variability in inhalation and nicotine absorption (Dawkins & Corcoran, 2014).

Our hypothesis that women would report greater liking and more positive oral sensations of flavored e-juice was partially supported. Women reported a strong liking for menthol, but no differences in sensations or preferences for any other flavors were found. Our finding is consistent with evidence that women are more likely to be menthol smokers than men (Villanti et al., 2016). Previously, we found that women experienced higher plasma nicotine concentrations with their preferred than non-preferred flavor of e-cigarette, while men showed no difference by flavor (Oncken et al., 2015). Other studies have shown that women are more susceptible to the sensory stimuli of smoking and more sensitive to the negative side effects of nicotine (e.g., nausea) than men (Kleykamp, Jennings, Sams, Weaver, & Eissenberg, 2008; Perkins et al., 2001; Zuo et al., 2015). Their preference for menthol may be partially explained by a genetic predisposition for heightened bitter taste perception (Oncken et al., 2015). Menthol can enhance nicotine exposure by stimulating greater depth of inhalation and impairing nicotine metabolism (Ahijevych & Garrett, 2004; Benowitz, Herrera, & Jacob, 2004), potentially making cessation more difficult. Given that flavor can affect the appeal and use patterns of e-cigarettes, further studies are needed to determine how flavorings may impact e-cigarette use differentially by sex.

To our knowledge, this is the first study to examine the association between e-cigarette flavor and ratings of sensations and liking by PROP taster phenotype. Supertasters (those with a heightened ability to taste bitterness) may need masking agents to suppress the bitter taste of substances, such as sweet additives to increase liking of bitter vegetables (Sharafi, Hayes, & Duffy, 2013). This hypothesis was partially supported in our study. Supertasters reported greater liking of menthol than unflavored e-cigarettes, even after controlling for sensory ratings. Future research could examine the interactive effect of taster phenotype and flavors on e-cigarette use over time.

A significant strength of this study includes the randomized design, in which each participant contributed data on every flavor and nicotine concentration combination. Furthermore, we recruited a relatively equal number of men and women, and had a good representation of non-menthol and minority smokers. Based on our previous work, we focused on ratings of bitter/sour, irritation, and sweet sensations. However, other sensations that may be important contributors to flavor preference were not captured. E-cigarette preference may be connected with its effects on nicotine delivery, as discussed above. However, we were not able to measure nicotine absorption. The study utilized commercially available e-liquids. We did not conduct chemical analyses to determine the levels of flavoring chemicals or free-base nicotine in the e-liquids or conduct sensory analysis of different levels of these chemicals on the liking of the vaped e-cigarettes. Finally, our sample consisted of regular, daily cigarette smokers with limited e-cigarette experience, and the findings may have limited generalizability to other groups.

5. Conclusions

This study is among the first to determine the effects of potentially sweet and masking flavors and nicotine content on perceptions of taste and liking of e-cigarettes among non-treatment-seeking smokers. It is also the first to examine differences by PROP taster phenotypes and in men and women. The results have significant implications for the

regulation and use of e-cigarettes for harm reduction and cessation strategies. Menthol flavoring may increase the palatability of e-cigarettes for non-treatment-seeking smokers. However, significant caution is warranted given the susceptibility of women and individuals with heightened taste ability to menthol, and the variability in flavorings and nicotine content in e-juices. Longitudinal research is needed to determine if menthol flavored e-cigarettes would generally hinder or help women and supertasters quit smoking cigarettes and become less nicotine dependent.

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Highlights:

- Cherry and chocolate were rated sweeter but not more liked than unflavored e-juice.
- Smokers rated menthol highest in liking, and this was especially true for women.
- PROP supertasting smokers liked menthol more than unflavored e-juice.
- Liking of high-nicotine e-juice was not altered by flavorings.
- Liking was enhanced by sweetness and blunted by irritation and bitterness/sourness

Figure 1.

Liking ratings as a function of e-cigarette flavorings and subject supertaster phenotype. Means adjusted for other sensory ratings, nicotine content of test e-cigarettes, and subject sex, menthol cigarette preference, and FTCD score. Super Taster vs. Medium Taster and Non-Taster: * $p < 0.05$

Table 1.

Average Ratings of Flavor Attributes (Bitter-Sour, Irritation, and Sweet Taste¹ and Liking²) of Unflavored and Flavored E-Cigarettes (Tobacco, Chocolate, Cherry, Menthol) With High (18mg/ml) and No Nicotine Content

Flavor Tested	Flavor Attribute											
	Bitter-Sour (N=132)				Irritation (N=132)				Sweet (N=132)			
	Overall	High Nicotine	No Nicotine		Overall	High Nicotine	No Nicotine		Overall	High Nicotine	No Nicotine	
Unflavored	Mean	4.83	4.86	4.80	6.07	6.72	5.42	8.13	8.38	7.88	9.77	7.89
	SD	9.23	9.52	8.96	11.4	12.4	10.4	11.0	11.5	10.6	31.8	33.2
	Range	0–53	0–53	0–40	0–60	0–60	0–55	0–65	0–65	0–52	–60–95	–60–95
Tobacco	Mean	6.32	6.01	6.62	6.75	7.02	6.48	9.52	10.3	8.74	14.1	15.0
	SD	11.2	11.2	11.3	13.6	12.6	14.5	12.6	13.0	12.1	32.7	34.4
	Range	0–55	0–55	0–55	0–95	0–55	0–95	0–60	0–60	0–60	–100–100	–100–95
Chocolate	Mean	5.17	5.71	4.62	4.75	4.87	4.64	12.3	13.3	11.3	8.88	6.65
	SD	9.82	10.9	8.58	8.93	8.80	9.10	12.5	13.5	11.4	33.6	33.1
	Range	0–50	0–50	0–50	0–52	0–50	0–52	0–70	0–70	0–55	–100–98	–85–95
Cherry	Mean	4.84	4.58	5.10	4.50	4.83	4.17	19.4	20.1	18.7	14.4	11.9
	SD	10.1	10.1	10.1	10.0	10.6	9.39	14.9	14.6	15.2	36.6	40.6
	Range	0–60	0–60	0–55	0–70	0–60	0–70	0–70	0–55	0–70	–100–100	–100–100
Menthol	Mean	6.07	5.69	6.45	5.75	6.67	4.83	10.6	10.8	10.4	17.9	17.2

Flavor Tested		Flavor Attribute												
	SD	10.1 9	10.3 3	10.0 7	11.9 2	13.1 8	10.4 8	13.1 7	13.4 7	12.9 2	37.2 6	36.0 3	38.5 7	
	Range	0 – 52	0 – 52	0 – 50	0 – 90	0 – 90	0 – 55	0 – 60	0 – 55	0 – 60	–100 –100	–90 – 95	–100 – 100	
Overall	Mean	—	5.37	5.52	—	6.02	5.11	—	12.6 1	11.4 2	—	14.3 2	11.7 6	
	SD	—	10.4 4	9.87	—	11.6 4	10.9 8	—	13.8 7	13.1 3	—	32.8 7	36.2 5	
	Range	—	0 – 60	0 – 55	—	0 – 90	0 – 95	—	0 – 70	0 – 70	—	–100 –100	–100 – 100	

¹ Taste was measured on gLMS scale from 0 (no sensation) to 100 (strongest imaginable sensation) with adjectives anchored on a logarithmic scale: 'barely detectable', (1.4), 'weak', (6), 'moderate', (17), 'strong', (35), and 'very strong' (53).

² Liking was measured on the following scale: Dislike (–100) to Like (100)

Table 2.

Summary of GEE and Mixed Model Analyses of Flavor Attributes as a Function of Flavor, Nicotine, and Baseline Characteristics.

Flavor attribute	Effect tested							
	Flavor (df=4)	Nicotine (df=1)	Flavor X Nicotine (df=4)	Age (df=1)	Sex (df=1)	Race (df=2)	Menthol Smoker (df= 1)	FTCD (df=1)
GEE Analyses ¹								
Bitter-Sour (ddf=1319)	10.08 *	2.36	0.87	1.53	7.23 **	0.97	1.57	0.14
Irritation (ddf=1319)	2.76	4.56 *	2.90	0.82	0.07	0.44	0.15	0.23
Mixed Model Analyses ²								
Sweet ³ (ddf=1178)	65.33 ***	4.27 *	0.50	2.09	3.26	3.07 *	0.17	0.72
Liking (ddf=1151)	3.76 **	2.26	0.51	0.68	1.32	5.31 ***	0.03	1.40

Note: FTCD= Fagerström Test for Cigarette Dependence df = numerator degrees of freedom; ddf = denominator degrees of freedom

*
 $p < 0.05$

**
 $p < 0.01$

 $p < 0.001$

¹ Bitter-Sour and Irritation were not normally distributed and were categorized as 0 (none) vs. 1 (any). For Bitter-Sour and Irritation, GEE analyses were conducted. Values shown are Wald χ^2 .

² For Sweet and Liking, mixed model analyses were conducted. Values shown are F values.

³ Sweet was square-root transformed.

Table 3.

Summary of GEE and Mixed Model Analyses of Flavor Attributes as a Function of Sex and Taster phenotype as Moderators.¹

		Flavor Attribute			
		GEE Analyses ²		Mixed Model Analyses ³	
	Effect Tested	Bitter-Sour	Irritation	Sweet	Liking
Model A	Flavor (df=4)	9.89 *	2.71	65.59 ***	3.75 **
	Sex (df=1)	7.37 **	0.08	3.26	1.32
	Flavor X Sex (df=4)	1.31	1.47	0.96	2.07
Model B	Nicotine (df=1)	2.38	4.68 *	4.16 *	2.00
	Sex (df=1)	7.33 **	0.06	3.25	1.32
	Nicotine X Sex (df=1)	0.06	2.18	2.95	0.02
Model C	Flavor (df=4)	8.15	1.18	55.73 ***	5.66 ***
	Taster phenotype (df=2)	1.31	0.45	3.12 *	0.36
	Flavor X Taster phenotype (df=8)	0.87	9.96	0.77	2.66 **
Model D	Nicotine (df=1)	1.22	4.58 *	5.07 *	0.86
	Taster phenotype (df=2)	1.25	0.59	3.12 *	0.36
	Nicotine X Taster phenotype (df=2)	0.10	1.05	1.64	0.40

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

¹ All models adjusted for flavor, nicotine content, age, race, menthol status, and FTCD

² For Bitter-Sour and Irritation, GEE analyses were conducted. Values shown are χ^2 .

³ For Sweet (transformed) and Liking, mixed model analyses were conducted. Values shown are F values.

Table 4.

Results of Mixed Model Analysis of Liking as a Function of Taste Sensations, Flavor, Flavor X Sex, Nicotine, Taster phenotype, Taster phenotype X Sex, and Baseline Characteristics.

Effect Tested	Liking		
	<i>df</i>	<i>ddf</i>	<i>F</i> value
Bitter-Sour	1	1122	26.85 ***
Irritation	1	1122	37.97 ***
Sweet ^I	1	1122	91.71 ***
Flavor	4	1122	9.89 ***
Sex	1	1122	1.66
Flavor X Sex	4	1122	1.91
Taster phenotype	2	1122	0.53
Flavor X Taster phenotype	8	1122	2.92 **
Nicotine Content	1	1122	1.74
Age	1	1122	0.69
Race	2	1122	4.04 *
Menthol Smoker	1	1122	0.50
FTCD	1	1122	1.55

Note: FTCD= Fagerström Test for Cigarette Dependence

df = numerator degrees of freedom; ddf = denominator degrees of freedom

*
 $p < 0.05$

**
 $p < 0.01$

 $p < 0.001$

^I Square-root Transformed