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Impact of e-liquid flavors on e-cigarette vaping behavior

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ABSTRACT

Objective: The primary objective of this pilot study was to describe the impact of e-cigarette liquid flavors on experienced e-cigarette users' vaping behavior.
Methods: 11 males and 3 females participated in a 3-day inpatient crossover study using e-cigarettes with strawberry, tobacco, and their usual brand e-liquid. Nicotine levels were nominally 18 mg/mL in the strawberry and tobacco e-liquids and ranged between 3–18 mg/mL in the usual brands. On each day, participants had access to the study e-cigarette (KangerTech mini ProTank 3, 1.5 Ohms, 3.7 V) and the assigned e-liquid during a 90-minute videotaped *ad libitum* session.
Results: Average puff duration was significantly longer when using the strawberry e-liquid (3.2 ± 1.3 s, mean ± SD) compared to the tobacco e-liquid (2.8 ± 1.1 s) but the average number of puffs was not significantly different (strawberry, 73 ± 35; tobacco, 69 ± 46). Compared to the strawberry- and tobacco-flavored e-liquids, average puff duration was significantly longer (4.3 ± 1.6 s) and the average number of puffs was significantly higher (106 ± 67 puffs) when participants used their usual brand of e-liquid. Participants generally puffed more frequently in small groups of puffs (1–5 puffs) with the strawberry compared to the tobacco e-liquid and more frequently in larger groups (> 10 puffs) with their usual brand. The strength of the relationship between vaping topography and nicotine intake and exposure were not consistent across e-liquids.
Conclusion: Vaping behavior changes across e-liquids and influences nicotine intake. Research is needed to understand the mechanisms that underlie these behavioral changes, including e-liquid pH and related sensory effects, subjective liking, and nicotine effects.

1. Introduction

The public health effects of electronic cigarettes (e-cigarettes), like other tobacco products, are strongly influenced by their dependency potential and abuse liability (Carter et al., 2009). A recent comprehensive review of the public health effects of e-cigarettes by the National Academies of Sciences, Engineering, and Medicine (NASEM) found substantial evidence that e-cigarette use results in symptoms of dependence on e-cigarettes (National Academies of Sciences Engineering and Medicine, 2018). Importantly, the report found moderate evidence that e-cigarette product characteristics contribute to the risk and severity of e-cigarette dependence (moderate evidence because the limitations of the studies reviewed, such as chance or bias, could not be ruled out). It is well established that nicotine is the primary pharmacological agent that causes dependence on combustible tobacco cigarettes (United States Department of Health and Human Services (USDHHS, 1988), and it is expected that nicotine plays a key role in e-cigarette dependency potential and abuse liability. Thus, understanding how various e-cigarette characteristics influence nicotine delivery and systemic exposure and, by extension, the dependency potential and abuse liability of e-cigarettes, may contribute to our understanding of the public health effects of e-cigarettes.

Studies show that e-cigarette characteristics, such as type of device, electrical power, and e-liquid nicotine content and flavors, influence nicotine delivery and systemic exposure (Farsalinos et al., 2014; Lopez et al., 2016; Ramôa et al., 2015; St.Helen et al., 2017; Wagener et al., 2016; Walele et al., 2016). For example, higher e-liquid nicotine content is associated with greater nicotine exposure for a given device (Lopez et al., 2016). How the devices are operated, such as vaping topography, also influences systemic exposure to nicotine (Dawkins et al.,

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2016; Farsalinos et al., 2015; National Academies of Sciences Engineering and Medicine, 2018; St.Helen et al., 2016b). For instance, longer puff duration leads to higher nicotine delivery for a given e-cigarette (Talih et al., 2015).

In addition, evidence suggests that user behavior (how the e-cigarette is used) changes with e-cigarette device characteristics, possibly as users engage in compensatory vaping to self-titrate their nicotine dose (Dawkins et al., 2016; Lopez et al., 2016; St.Helen et al., 2017) or because of subjective flavor liking and sensory effects (Goldenson et al., 2016). Dawkins et al. (2016) showed that the number of puffs taken and the duration of puffs change with different nicotine concentrations of e-liquids; experienced users puff more frequently, take longer puffs, and consume more e-liquid when vaping low compared to high nicotine content e-liquids. Lopez et al. (2016) found similar results in a study of e-cigarette-naïve combustible cigarette smokers who vaped e-liquids with different nicotine levels.

The influence of e-liquid flavors on user behavior and systemic exposure to nicotine is not well defined. Of the published studies on e-cigarette vaping topography in human subjects to date (Behar et al., 2015; Cunningham et al., 2016; Dawkins et al., 2016; Farsalinos et al., 2015; Goniewicz et al., 2013; Lee et al., 2015; Lopez et al., 2016; Norton et al., 2014; Robinson et al., 2015, 2016; Spindle et al., 2015, 2017; St.Helen et al., 2016b; Strasser et al., 2016), none of the studies described whether users change their vaping behavior across different e-liquid flavors. If users change their vaping behavior across flavors, other questions need to be answered, such as: (1) what aspect(s) of their vaping behavior, including vaping topography and vaping pattern, do users change; (2) how does the change in vaping behavior affect systemic exposure to nicotine; and (3) what mechanisms underlie the change in vaping behavior?

Vaping topography consists of a range of parameters, such as number of puffs, inter-puff interval, puff duration, puff volume, and puff velocity. Vaping pattern includes how users group or cluster their puffs. We have shown previously that e-cigarette users vape their e-cigarettes intermittently, taking a majority of their puffs in small groups of puffs during *ad libitum* access, which results in a gradual increase in blood nicotine levels rather than rapid peaks (St.Helen et al., 2016b). Alternatively, users can take several puffs in close proximity (cluster of puffs), which delivers nicotine in a near-bolus dose, resulting in rapid peak blood nicotine levels (St.Helen et al., 2017, 2016a). In this report, we present findings from a pilot study that assessed whether vaping topography and vaping patterns change across e-liquid flavors and how the changes influenced exposure to nicotine. Our findings provide supportive evidence for further research on potential mechanisms underlying changes in vaping behavior.

2. Methods

We conducted a three-arm crossover study on the effects of flavors on e-cigarette pharmacology in experienced e-cigarette users. In a previous publication, we described the study details and presented the effects of flavors on nicotine intake, systemic nicotine retention, and physiologic and subjective effects during controlled and *ad libitum* use of e-cigarettes (St.Helen et al., 2017). The current manuscript focuses on the effect of flavors on vaping topography and patterns of use during the period of *ad libitum* access.

2.1. Participants

The study included a convenience sample of 14 participants (3 females, 11 males) whom we recruited *via* Craigslist.com and flyers in the neighboring communities, vape shops, and on college campuses. Criteria for eligibility included: exclusive e-cigarette use or dual use of fewer than five combustible tobacco cigarettes per day; use of second and/or third generation e-cigarettes on at least 25 days per month over the past three months or more; saliva cotinine level of at least 30 ng/mL; and expired carbon monoxide (expired CO) of 8 ppm or less. Participants who also smoked combustible cigarettes were asked to abstain overnight before coming to the screening visit. This was done in order to determine whether they were able to abstain from cigarette smoking since they would not be allowed to smoke combustible cigarettes for the duration of the study. Participants with any of the following were excluded: unstable chronic medical conditions; current or past severe mental illness; pregnant; current illicit substance use other than cannabis; and people who only used first generation e-cigarettes. The study was approved by the Institutional Review Board at the University of California San Francisco. Written, informed consent was obtained from each participant and all participants were financially compensated.

2.2. Study e-cigarette and e-liquid flavor conditions

This crossover study had three experimental arms. Participants used either a strawberry, tobacco or their usual brand flavor of e-liquid exclusively in each arm. We purchased the strawberry and tobacco test e-liquids from Bulkejuice.com. Both e-liquids were labeled 50/50 V G/PG (vegetable glycerin/propylene glycol) and 18 mg/mL nicotine. The measured nicotine and VG/PG ratio for the strawberry e-liquid were 19.9 mg/mL and 60/40, respectively, and 19.3 mg/mL and 56/44, respectively, for the tobacco e-liquid. The measured nicotine concentrations of the usual e-liquids averaged 7.4 mg/mL (SD 5.3) (range 1.6–16.7 mg/mL) (range on labels: 3–18 mg/mL). The mean VG/PG ratio for the usual brand e-liquids was 63/37 with a range of 31/69–95/5. The pH of the strawberry and tobacco e-liquids was 8.29 and 9.10, respectively, while the average pH of the usual brand of e-liquids was 6.80 ± 1.58 (mean ± SD) (range, 4.33–8.97). We measured the pH of the e-liquids using an Accumet AB15 pH meter (Fisher Scientific, Waltham, MA). For each measurement, 0.5 g of each e-liquid was mixed with 4.5 mL of deionized water to form a 1:10 dilution of nicotine.

The study e-cigarette devices were KangerTech Mini ProTank 3 clearomizers (1.5 ohms) connected to a KangerTech 3.7 V, 1000 mA h battery, and were purchased directly from Kangertech.com. Participants used a new clearomizer (tank) for each assigned flavor. The electrical power of the e-cigarettes was 9.1 W.

2.3. Study procedures

We conducted the three-day inpatient study on the Clinical Research Center (CRC) research ward at Zuckerberg San Francisco General Hospital. Each of the three study days ran from about 4 P M. to 4 P M. of the next day. From 4–10 P.M. (Acclimatization Session), participants could vape *ad libitum* the e-liquid assigned for the next day's procedures to become acclimatized to the e-liquid. Participants were abstinent overnight until the morning standardized session of 15 puffs, which was followed by four hours of abstinence, and then a 90-minute *ad libitum* use session.

After the four hours of abstinence following the standardized session of 15 puffs, we administered subjective questionnaires and obtained a blood sample from the participants. We filled the e-cigarette tank to approximately the same level each time with the same e-liquid used during the standardized session. To determine the amount of e-liquid consumed, we weighed the e-cigarette tank (without the battery) before and after the session using a microbalance (Mettler Toledo MS104S, 0.0001 g readability). Starting at 2:00 P.M., we instructed participants to vape the study e-cigarette as desired over a 90-minute period. During that time, participants watched television, browsed the Internet through their personal computers or smartphones and/or read books. We did not allow participants to sleep or doze off. Blood samples were collected every 15 min, and study personnel administered subjective questionnaires at the end of the 90-minute session. One of the questionnaires that we administered was the modified Cigarette Evaluation Questionnaire (mCEQ), further modified for e-cigarettes (Cappelleri