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Drug and alcohol dependence acute effects of pod-style e-cigarettes in vaping-naïve smokers

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Abstract

Background: This study investigated the acute effects of exposure to pod-style e-cigarettes on subjective, behavioral, and physiological outcomes indicative of the potential to encourage vaping-naïve smokers to switch to e-cigarettes.

Methods: In a within-subject experiment, never-vaping adult smokers interested in trying e-cigarettes (n=24) completed 4 laboratory visits following 16-hr tobacco abstinence. Visits involved controlled puffing from preferred brand cigarettes (OwnCig) or a standardized pod-style e-cigarette with either no nicotine (NoNic), nicotine freebase (NicFreebase; 0.5% nicotine concentration), or nicotine salt (NicSalt E-Cig; 2.8% concentration) solutions. Outcomes included smoking urge, mood, user experience, plasma nicotine, and a behavioral task assessing ability to delay smoking.

Results: NoNic, NicFreebase, and NicSalt pod-style e-cigarettes were significantly less effective than OwnCig at reducing smoking urge and increasing plasma nicotine, positive affect, satisfying user experience ratings, and ability to delay smoking on the behavioral task. Differences among pod-style e-cigarette conditions were limited to: (a) NicFreebase (vs. NoNic) preferentially suppressed participants' urge to smoke to alleviate negative mood, (b) NicFreebase (vs. NicSalt) slightly preferentially increased plasma nicotine; and (c) NicFreebase and NicSalt (vs. NoNic) produced higher aversive user experience ratings.

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Conflict of Interest: None.

Conclusions: In tobacco deprived smokers' initial vaping experience, controlled administration of certain pod-style e-cigarettes with 0.5% NicFreebase or 2.8% NicSalt may be deficient comparators to cigarettes in terms of their capacity to acutely improve mood, deliver nicotine, suppress smoking motivation, and offer a satisfying user experience. Future research is needed to test pod-style e-cigarettes with higher nicotine doses and confirm whether NicFreebase vs. NicSalt enhances nicotine absorption.

Keywords

E-cigarette; Nicotine formulation; Switching; Smoking

1.0 Introduction

Smokers switching from combustible cigarettes to electronic cigarettes (e-cigarettes) might experience reduced harm, especially if they quit smoking entirely (National Academies of Sciences, Engineering, and Medicine et al., 2018). Clinical laboratory research is useful for isolating how different types of e-cigarettes acutely affect outcomes relevant to switching behavior, such as nicotine absorption, satisfaction with user experience, and motivation for smoking cigarettes. If particular e-cigarette products show promise for promoting switching behavior in the clinical laboratory, regulatory policies allowing such products to remain on the marketplace may benefit smokers' health.

The types of e-cigarettes on the market have rapidly shifted and pod-style e-cigarettes now occupy the majority of e-cigarette sales in some countries (Romberg et al., 2019). The defining characteristics of pod-style e-cigarettes include their diminutive size, modest electrical power output, and small reservoirs for e-cigarette solutions (i.e., "pods") that typically include nicotine salt (NicSalt) formulations (Barrington-Trimis and Leventhal, 2018). To create NicSalt formulations, manufacturers insert acid additives, which protonates nicotine molecules, causing nicotine to change from freebase to salt chemical form (Harvanko et al., 2020). Several characteristics that distinguish NicSalt and NicFreebase formulations might differentiate their effects on the user experience and other outcomes relevant to switching behavior. Users might perceive NicSalt formulations as less harsh compared to solutions without acid additives that contain NicFreebase (Barrington-Trimis and Leventhal, 2018; Tackett et al., 2020). NicSalt vs. NicFreebase may be less likely to permeate biological membrane which might reduce oropharyngeal nicotine absorption (Gholap et al., 2020; Shao and Friedman, 2020).

Most prior clinical laboratory research on the acute effects of e-cigarettes have tested cig-a-likes, tank-style devices, and other older e-cigarette models (National Academies of Sciences, Engineering, and Medicine et al., 2018). Besides tobacco industry research (Goldenson et al., 2021a, 2021b, 2021c, 2020; O'Connell et al., 2019), most clinical laboratory evidence on pod-style cigarettes include people who already use e-cigarettes and have pre-existing preferences (e.g., Hajek et al., 2014; Phillips-Waller et al., 2021; Yingst et al., 2019). Studying samples of vaping naïve smokers is important for identifying the effects of pod-style e-cigarettes among individuals without pre-existing preferences for e-cigarettes. A recent clinical laboratory study of pod-style e-cigarettes among vaping-naïve smokers

found that JUUL brand pod-style e-cigarettes provided less nicotine delivery, smoking urge suppression, and subjective satisfaction than own brand cigarettes (Maloney et al., 2020). What is still unknown is whether pod-style e-cigarettes affect actual smoking behavior and whether NicSalt and NicFreebase formulations differentiate the acute effects of pod-style products on outcomes relevant to switching behavior in e-cigarette naïve smokers. Such evidence is needed to inform whether recent and proposed regulatory policies to limit availability of pod-style e-cigarettes with NicSalt formulations to prevent youth use (Tackett et al., 2020; U.S. Food and Drug Administration, 2020) might be disadvantageous for adult smokers seeking e-cigarettes as a less harmful tobacco product substitute.

This clinical laboratory study of e-cigarette naïve older adult smokers with moderate nicotine dependence interested in trying e-cigarettes examined the acute effects of exposure to pod-style e-cigarettes on outcomes relevant to switching behavior after overnight tobacco abstinence. We compared pod-style e-cigarettes with either NicSalt, NicFreebase, or no nicotine (NoNic) solutions to one another and to participants' own brand cigarettes (OwnCigs). Based on prior research (Maloney et al., 2020), we hypothesized that OwnCigs would more robustly increase blood nicotine levels, enhance mood, reduce smoking urge, suppress smoking on a behavioral smoking task, and offer a satisfying user experience compared to each pod-style e-cigarette. Additionally, we hypothesized that pod-style e-cigarettes with solutions containing nicotine in some form (NicSalt or NicFreebase) versus NoNic solutions would more robustly suppress smoking urge and behavior, improve mood, and result in higher satisfying user experience ratings. Finally, we hypothesized that NicSalt vs. NicFreebase would produce more desirable airway sensations (i.e., less harshness, more smoothness).

2.0 Methods

2.1 Participants

Participants (n=24) were recruited from Los Angeles, California, USA via online advertisements. Inclusion criteria included: (a) >21 years of age; (b) daily cigarette smoking for ≥2 years; (c) currently smoke >4 cigarettes/day; (d) never tried e-cigarettes; (e) interest in trying e-cigarettes; and (f) breath carbon monoxide level >10ppm at intake (to verify smoking status). Exclusion criteria were: (a) impending plan to quit using nicotine/tobacco products within the next 30 days (because study procedures required smoking); (b) currently/planning to become pregnant/breastfeeding; (c) current daily use of tobacco products besides combustible cigarettes; and (d) positive breath alcohol at intake. Participants provided written informed consent and were compensated $385 for study completion. University of Southern California Institutional Review Board approved the protocol.

2.2 Design

In a within-subject single factor design, all participants completed the 4 study conditions (NoNic E-Cig, NicFreebase E-cig, Nic Salt E-cig, and OwnCig) on 4 separate visits in random order. At each visit, participants completed a standardized tobacco product administration protocol involving either the e-cigarette device with the respective

experimental condition's solution or their preferred brand cigarette and an outcome measure battery that was identical across visits.

2.3 Materials and Assay of E-Cigarette Solutions

A commercially marketed e-cigarette solution in watermelon flavor available in equivalent NoNic, NicFreebase, and NicSalt versions was used (Suorin BlowSauce-DripFire; City of Industry, California, USA). These were selected based on consumer reviews and research indicating preferences for fruit flavors in smokers that switch to vaping (Russell et al., 2018). To increase internal validity that differences amongst the three e-cigarette conditions were caused by the presence and type of nicotine, we used the same device and the same e-liquid flavor and manufacturer across conditions. Because freebase nicotine solutions are typically marketed at concentrations from 0.1% to 1.0%, we selected 0.5% NicFreebase. This helped provide a NicFreebase condition that is representative of many free-based nicotine products sold on the market. Because nicotine salt solutions are marketed in concentrations from 2%−7% and the European Union regulations limit nicotine concentration to 20mg/ml, we selected a nicotine concentration toward the low end of the spectrum (2.8%) for the NicSalt condition. This permitted us to make inferences that might be relevant to the conditions of the European Union while also being sold in North American. Constituents in the solutions were assayed by the Roswell Park Comprehensive Cancer Center Nicotine and Tobacco Product Assessment Core using chromatography with a nitrogen-phosphorous detector per previously-published methods (Leigh et al., 2016). Assays confirmed the presence of benzoic acid in only the NicSalt solution as well as provided nicotine concentration (NoNic: 0%, NicFreebase: 0.5%, NicSalt: 2.8%), density (NoNic: 1.18g/ml; NicFreebase: 1.18 g/ml; NicSalt: 1.16 g/ml), and PG/VG ratio (NoNic: 35/65; NicFreebase: 30/70, NicSalt: 45/55) estimates. While PG/VG ratios were different among the studied solutions, recent work suggests varying PG/VG ratios have little impact on the subjective and reinforcing effects of e-cigarettes among vaping-naïve smokers (Smith et al., 2020). For each e-cigarette condition, we used the same Suorin iShare Pod System Device (7W; 2.0Ω resistance; 130 mAh built-in battery), which is similar in size and shape to other widely sold pod-style e-cigarettes (e.g., JUUL) and equipped with pod cartridge inserts that can be (re)filled.

2.4 Procedure

After phone screening, participants attended an intake visit involving informed consent and eligibility assessment, including pregnancy test, CO breath, and alcohol breath analysis. Eligible participants then completed demographic and tobacco product use history questionnaires and were given the opportunity to practice using the study e-cigarette device with a NoNic flavorless solution. Participants then attended four experimental visits each scheduled around noon and were instructed to abstain from using nicotine/tobacco products for 16-hours and psychoactive substances for 24 hours prior to each visit. Visits were scheduled to occur at least 24 hours apart from one another.

At each experimental visit outset, participants provided breath samples to verify smoking (CO<10 ppm) and alcohol (BrAC=0) abstinence. Participants with BrAC or CO levels greater than the cutoffs were allowed to complete the respective visit again on a future

day (n=2, each of whom met abstinence criteria on the second attempt). Next, participants completed pre-exposure subjective and physiological measures of study outcomes (see below) and blood was drawn roughly half an hour into the visit. Participants then completed the standardized self-administration tobacco product exposure using the respective study condition's product. To increase internal validity of conclusions that differences in outcomes were due to the product and confounded by differences in the amount of aerosol inhaled, we used a guided controlled puffing procedure that standardized puffing behavior across all participants and conditions. Each puff cycle had a 10-second preparation, 4-second inhalation, 1-second hold, and 2-second exhale interval with 23 seconds between each puff cycle and was accompanied by a video that cued participants when to inhale and exhale per prior work (Goldenson et al., 2016; Leventhal et al., 2019). Participants then immediately completed a post-exposure assessment, which included all pre-exposure measures and additional self-report user experience and sensory ratings of the product they administered. Additionally, post-exposure blood was drawn five minutes after product administration. The experimental visits concluded with a behavioral smoking task conducted in the laboratory suite equipped with ventilation systems to clear smoke.

2.5 Baseline Visit Measures

Participants completed author-constructed demographic and tobacco product use history questionnaires (see responses in Table 1) and the Fagerström Test for Cigarette Dependence (FTCD; Heatherton et al., 1991). Exhaled carbon monoxide (Vitalograph, Lenexa, KS) provided baseline combustible tobacco exposure data.

2.6 Experimental Visit Measures

2.6.1 Smoking Urge.—

During pre- and post-exposure assessments, participants completed the 10-item Brief Questionnaire of Smoking Urges (QSU; Cox et al., 2001), which includes self-statements assessing desire to smoke for pleasure and intention to smoke (Factor 1; e.g., "I have an urge for a cigarette.") and desire to smoke to alleviate negative mood (Factor 2; e.g., "I would control things better if I could smoke."). Participants rate agreement based on how they felt "right now" on 6-point Likert scales (0=Strongly disagree to 5=Strongly agree). Mean scores for each factor were calculated with higher scores representing higher urge (Chronbach's αs>0.94).

2.6.2 Mood.—

At pre- and post-exposure assessments, participants completed the Positive and Negative Affect Scale (PANAS; Watson et al., 1988), which includes positive (10-items; αs:.93-.95) and negative (10-items; αs:.88-.91) affect subscales assessing how they feel "right now" on 5-point scale (1=Not at all to 5=Extremely). Mean scores were calculated for each subscale; higher scores indicate higher affect intensity.

2.6.3 Tobacco Product Evaluation User Experience Ratings.—

During post-exposure assessments, participants completed a previously-validated scale (Cappelleri et al., 2007; Westman et al., 1992), assessing user experiences applicable to cigarettes and other tobacco products. Items were rated on 100-point visual analogue scales and constitute five subscales, each calculated as the mean rating per item: satisfaction ("Satisfying" and "Taste good"; α=.84), psychological reward ("Calm you down," "Help you concentrate" "Make

you feel more awake?" "Reduce hunger?" "Make you feel less irritable?"; α=.91), aversion ("Make you nauseated?" "Make you dizzy?"; α=.63), sensory enjoyment ("Enjoy sensations in throat and chest"), and cigarette craving reduction ("Reduce cigarette craving") subscales (Westman et al., 1992). Higher scores indicate higher intensity perceived user experience.

2.6.4 E-Cigarette Sensory Attribute Ratings.—During post-exposure assessments for the three E-Cig conditions, participants completed 4 ratings designed to reflect the sensory attributes of e-cigarette products on visual analogue scales (0–100 range; sweetness, smoothness, bitterness, and harshness) as in prior work (Leventhal et al., 2019). Based on previous factor analytic research (Leventhal et al., 2019), each sensory item was analyzed as a separate outcome, with higher ratings representing higher intensity sensations. Criterion and convergent validity of e-cigarette sensory attribute ratings are supported by previous research showing associations of higher smoothness and sweetness and lower harshness and bitterness with higher product appeal and willingness to use the product again (Leventhal et al., 2019).

2.6.5 Physiological Measures.—At pre-and post-exposure assessments, heart rate was assessed via a digital sphygmomanometer (Panasonic; Cypress, CA, USA) and 12mL of venipuncture blood was collected for plasma nicotine. Plasma nicotine was determined via gas chromatography with nitrogen-phosphorus detection (Jacob et al., 1981), using 5-methylnicotine and 1-methyl-5-(2-pyridyl)-pyrrolidin-2-one as internal standards using the UCSF nicotine biomarker core. This method was modified for simultaneous extraction of nicotine with determination using capillary gas chromatography (Jacob et al., 1991). The limits of quantification were 1 ng/ml.

2.6.6 Behavioral Smoking Task.—This behavioral economics-based task measures the motivation to smoke under conditions in which avoiding smoking is monetarily rewarded (Cortland et al., 2019). Beginning with the task's delay portion, participants were instructed that they could smoke their preferred brand cigarettes at any point within the next 50 minutes, but for each 5 minutes that they delayed smoking, they would earn $0.50 for a maximum of $5.00. The delay period ended when participants indicated they wished to smoke or after all 50 minutes elapsed; hence, no smoking occurred during the delay portion of the task. Immediately after the delay portion ended, participants then began the task's self-administration portion for which they were instructed that they could smoke as many cigarettes as they wished for the next 60 minutes, they had a $4.00 credit, each cigarette smoked would subtract $0.50, and there was no further opportunity to smoke until visit end (120–170 min later) to prevent any impending opportunity to smoke from influencing task smoking choices. Latency to smoking initiation during the delay portion (range: 0–50 minutes) and number of cigarettes purchased during the self-administration portion (range: 0–8) were outcomes. Previous studies support the validity of this task as an analogue model of smoking motivation, reliably showing changes in task performance due to deprivation (Pang and Leventhal, 2013), stress (Ameringer and Leventhal, 2015), and cessation medication (McKee, 2009) in expected directions. Monetary values were based on prior studies among smokers from the local population resulting in sufficient deprivation

effects and inter-individual variance (Aguirre et al., 2015; Ameringer and Leventhal, 2015; Pang and Leventhal, 2013).

2.7 Data Analysis

After descriptive analyses, primary analyses used generalized estimating equations (GEEs) for linear modeling with continuous outcome distributions (Zeger et al., 1988), which accounted for participant-level data clustering with separate models for each outcome. In contrast with missing data approaches requiring participant-level deletion, GEEs include all available observations within participants across all four experimental visits, which was necessary due to missing data on certain outcomes on some visits (e.g., venipuncture unsuccessful). Each model included the independent categorical within-subject variable of study condition (NoNic vs. NicFreebase vs. NicSalt vs. OwnCig). To model exposure-induced changes in outcomes administered at pre- and post-product exposure assessments, GEEs predicting post-exposure outcomes were adjusted for respective pre-exposure values and estimated marginal means were calculated. For outcomes with significant omnibus study condition effects, pairwise contrasts were conducted. Analyses were conducted using IBM SPSS Statistics Version 25 (IBM Corp, 2017). Significance was .05 (2-tailed).

3.0 Results

3.1 Descriptive Results

Of 59 individuals screened in-person, 45 were eligible, of whom 24 completed all four experimental visits and were included in the analytic sample. The sample (67% male; *M*[SD] age=51[10.7] years) was racially/ethnically heterogeneous (Table 1). On average, participants had moderate mean levels of nicotine dependence (FTCD score=5.0[SD=2.0]) and smoked 15.6 (SD=11.9) cigarettes per day.

3.2 Primary Results

3.2.1 Subjective outcomes.—Significant omnibus differences in post-exposure positive affect across study conditions were found (Table 2). After adjusting for pre-product exposure scores, estimated marginal means from post-hoc pairwise comparisons showed that OwnCigs (*M* score=31.9) more robustly increased positive affect relative to NoNic E-Cigs (*M*=29.7) but no other significant pairwise differences. Negative affect did not differ by study conditions. Product condition differentially affected QSU Factor 1 (intention to smoke and urge to smoke for pleasure), such that OwnCig (post-exposure *M*=2.0) reduced urge more than each of the E-Cig conditions (*M*s: NoNic=3.2; NicFreebase=3.0; NicSalt=3.0), which did not differ from one another. QSU Factor 2 (urge to smoke to alleviate negative mood) was more robustly reduced by OwnCig (*M*=1.1) relative to NicSalt (*M*=1.7) or NoNic (*M*=2.0) E-Cigs and more strongly reduced by NicFreebase (*M*=1.6) vs. NoNic (*M*=2.0) E-Cigs.

Study condition significantly affected all tobacco product evaluation user experience subscales in omnibus tests. For each desirable user experience effect subscale (Satisfaction, Reward, Enjoyment, Craving Reduction), OwnCig produced more positive ratings than each of the three E-Cig conditions, which typically did not differ from each other in

pairwise tests (see Table 2). Aversion subscale scores were higher for all 3 nicotine-containing products (*M*s: NicFreebase=31.2, NicSalt=31.4, OwnCig=35.0) than NoNic E-Cigs (*M*=13.7). Comparison of e-cigarette sensory attribute ratings found significant differences across the 3 E-Cig conditions in smoothness and harshness but not bitterness or sweetness. Pairwise contrasts found that both NicFreebase and NicSalt E-Cigs were rated as harsher and less smooth than NoNic E-Cigs but did not differ from one another (Table 2).

3.2.2 Physiological outcomes.—Changes in heart rate differed by study condition. The three nicotine containing products significantly increased heart rate (*M* bpm: NicFreebase=75.2; NicSalt=72.5; OwnCig=74.0) vs. NoNic E-Cigs (*M*=68.0 bpm) but did not differ from one another in pairwise tests. Significant pairwise differences across each of the four study conditions were found for increases in plasma nicotine levels. Nicotine (ng/mL) marginal means were significantly higher after exposure to OwnCig (*M*=10.9), followed by NicFreebase (*M*=2.7), NicSalt (*M*=1.6), and NoNic (*M*=0.7) E-Cigs, respectively.

3.2.3 Behavioral smoking task outcomes.—Study conditions significantly affected latency to smoking initiation during the task's delay period. Participants delayed smoking initiation for a significantly longer number of minutes after administering OwnCig (*M*=28.9) compared to either NoNic (*M*=19.9) or NicFreebase (*M*=21.2) E-Cigs, but no other pairwise contrasts in smoking latency were significant. Study conditions did not affect the number of cigarettes smoked during the task's self-administration period (Table 2).

4.0 Discussion

In this clinical laboratory study of vaping-naïve older adult smokers with moderate nicotine dependence, OwnCigs outperformed a pod-style e-cigarette device with either 0.5% NicFreebase, 2.8% NicSalt, or NoNic solutions in nicotine delivery, positive mood enhancement, and user experience satisfaction ratings. There were few differences between 0.5% NicFreebase, 2.8% NicSalt, and NoNic study conditions on outcomes potentially indicative of whether pod-style e-cigarettes are viable cigarette substitutes that could promote switching. Neither the NicSalt nor NicFreebase solutions in the pod-style e-cigarettes used in the current study consistently or robustly suppressed smoking urge or behavior relative to one another or relative to NoNic E-Cigs, with the single exception that NicFreebase (vs. NoNic) E-Cig conditions preferentially suppressed participants' urge to smoke to alleviate negative mood.

One reason why NicSalt or NicFreebase E-Cigs in this study had weaker subjective effects than OwnCigs among older, moderately dependent smokers was likely because both delivered modest amounts of nicotine, thus findings from this study should be considered with this in mind. While the nicotine concentrations of study products were within (for NicFreebase) or slightly exceeding (for NicSalt) European Union regulatory limits on e-cigarette nicotine concentration and are widely marketed, high NicSalt concentrations (~5%) are widely sold in North America (2.8% concentration) (Romberg et al., 2019). A previous study among vaping-naïve smokers that used procedures similar to the current study found that 5% JUUL pod-style e-cigarettes delivered significantly less nicotine than own

brand cigarettes (Maloney et al., 2020). The modest nicotine yield from NicSalt pod-style e-cigarettes older vaping-naïve smokers might get upon first experience with e-cigarettes and other factors may explain why some smokers do not switch to e-cigarettes (McKeganey and Dickson, 2017). Vaping-naïve older smokers may not be accustomed to the type of puffing topography required to yield substantial nicotine levels from e-cigarettes, which might explain why the nicotine yield was low for both the NicFreebase and NicSalt solutions in this study. Previous clinical laboratory studies of experienced vapers find nicotine yield from JUUL to be substantial and similar to cigarettes (Hajek et al., 2014; Yingst et al., 2019).

While both nicotine-containing pod-style e-cigarettes delivered modest amounts of nicotine in this study, NicSalt delivered slightly less blood nicotine than the NicFreebase product despite having higher nicotine concentrations (2.8% vs. 0.5%). A 0.5% nicotine concentration solution might be expected to deliver modest levels of plasma nicotine (regardless of whether NicSalt or NicFreebase formulation) if loaded into pod-style e-cigarette devices, which often output weak electrical power (Gholap et al., 2020). The lower plasma nicotine yield from the NicSalt vs. NicFreebase product in this study might reflect the fact that protonated nicotine might less easily permeate the oropharyngeal biological membrane than unprotonated nicotine, which could promote lower nicotine absorption (Gholap et al., 2020; Shao and Friedman, 2020). If replicated, this finding might reflect an important fundamental difference in nicotine delivery between NicSalt and NicFreebase, per se, that can be parsed from other factors that influence nicotine delivery, such as puffing topography, device power, or other constituents. It is unlikely that differences in the amount of aerosol inhaled account for the NicFreebase vs. NicSalt differences in blood nicotine in this study because a controlled puffing procedure was used, which standardized puff duration, count, and inter-puff interval. The NicFreebase vs. NicSalt differences are also not accounted for by study device or e-liquid flavor given those were experimentally constrained to be equal in this experiment. While this design is useful for enhancing the internal validity of the results, there is a tradeoff for ecological validity because the standardized puffing protocol might not represent naturalistic ad lib vaping patterns and NicFreebase is commonly with powerful non-pod devices.

Besides plasma nicotine, the outcomes in which the three e-liquids differed from one another were those that represent nicotine’s acute physiological and sensory effects. Compared to NoNic, NicSalt and NicFreebase solutions increased heart rate and were rated as harsher and less smooth among older smokers with moderate nicotine dependence. Stimulation of nicotinic acetylcholine receptors lining the airways by nicotine likely increases sensations of harshness and reduces perceived smoothness from tobacco product aerosol (Lee et al., 2007), and high smoothness and low harshness correlate with perceived product appeal in previous research (Leventhal et al., 2019). Despite that NicSalt generates aerosol that is less harsh than NicFreebase (Leventhal et al., 2021), there were no differences in airway sensations of the two nicotine-containing e-cigarettes among the older, modestly dependent smokers in this study. A major caveat, however, is that the nicotine concentration of the study’s NicSalt product was substantially higher than the NicFreebase product, a difference representative of actual marketplace. Manufacturers typically sell NicSalt products at nicotine concentration levels much higher than NicFreebase products, likely given the

expectation that users may pair NicFreebase solutions with powerful devices (Gholap et al., 2020). Under conditions in which nicotine concentration is held constant, NicSalt and NicFreebase products indeed produce different sensory attributes (Leventhal et al., 2021).

There are limitations in the study. First, this study used products from a single e-cigarette brand because they sold comparative NicSalt, NicFreebase, and NoNic solutions that were compatible with a common pod-style device, which increased internal validity that differences across study conditions were due to nicotine presence and type, per se. It is unknown whether these results would generalize to other pod-style products or how pod-style e-cigarettes compare to tank or other e-cigarette types. Relatedly, future studies utilizing NicSalt and NicFreebase products with equal nicotine concentration would be useful to isolate the effects of nicotine formulation. Third, product exposure involved a standardized sequence. Future studies should incorporate both standardized and ad libitum puffing procedures to determine if user-determined puffing patterns might be needed to optimize user satisfaction and increase substitutability to OwnCigs. Fourth, the paradigm and its measures represent an experimental analogue in a clinical laboratory setting, which may not entirely correspond with actual switching behavior in the natural ecology. Fifth, because the duration of the delay during the behavioral smoking task is selected by the participant, there is the possibility of confounding of the total duration of >16 hours combustible cigarette deprivation by an additional 0–50 minutes of systematic variance, which could affect smoking behaviors during the self-administration portion of the task. Finally, the sample was constituted by older smokers with moderate level of nicotine dependence and chronic smoking histories, on average. In some respects this population is similar to the population of smokers who have not switched to vaping who tend to be older adults (Mayer et al., 2020). However, the current results might not generalize to populations of younger smokers, smokers with severe nicotine dependence, non-daily and non-dependent smokers, and individuals with significant experience using e-cigarettes.

5.0 Conclusions

In this clinical laboratory study in a sample of smokers who were, on average, middle aged and had moderate severity nicotine dependence, the acute effects of controlled self-administration of a pod-style e-cigarette device with 0.5% NicFreebase, 2.8% NicSalt, or NoNic fruit-flavored solutions were deficient comparators to OwnCigs. This study also provides new evidence that NicFreebase might deliver higher nicotine yield than NicSalt, holding constant variation in device and other factors. Further studies of whether higher nicotine concentration, flavor or other product characteristics, and user factors moderate the acute effects of pod-style e-cigarettes are warranted to fully assess the potential of these products to promote switching from combustible to e-cigarettes.

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Data Availability Statement:

Data will be made available upon request.

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Highlights

- Cigs outperformed 0.5% Freebase & 2.8% Salt nicotine pod e-cigs
- 0.5% Freebase v. 2.8% Salt pod e-cigs caused slightly higher blood nicotine
- Further testing of different nicotine+e-cig device combinations warranted

Table 1.

Descriptive Statistics of Participant Characteristics

Variable	M (SD) or N (%)
Demographics	
Female, N (%)	8 (33.3)
Age, M (SD), years	51.3 (10.7)
Race, N (%)	
White	7 (29.2)
Black	13 (54.2)
Multi-Racial	1 (4.2)
Other [†]	3 (12.5)
Hispanic ethnicity, N (%)	4 (16.7)
Education	
High school diploma or GED	9 (37.5)
Some college completed or currently in college	11 (45.8)
College degree or higher	4 (16.7)
Smoking characteristics	
Carbon monoxide at intake visit, M (SD), ppm	16.7 (5.5)
Age started smoking every day, M (SD), years	19.4 (10.6)
Current cigarettes smoked per day, M (SD)	15.6 (11.9)
Cigarettes/day when smoking heaviest, M (SD)	25.1 (16.7)
FTCD, M (SD)	5.0 (2.0)

Note. $n = 24$. Sample size ranges from 23 – 24 across variables due to differential patterns of missing data across variables. FTCD = Fagerström Test for Cigarette Dependence; ppm = parts per million.

[†]Includes “American Indian or Alaskan Native”, “Middle Eastern”, “Pacific Islander (including Hawaii)”, and “Other”.

Table 2

Marginal means (SEs) of outcomes by study condition.

Outcome Variable	Omnibus test, X^2[†]	NoNic e-cig, M (SE)	NicFreebase e-cig, M (SE)	NicSalt e-Cig, M (SE)	Own brand cigarette, M (SE)	Pairwise Comparisons[#]
PANAS Positive Affect	8.0*	29.7 (1.1)	29.8 (1.2)	30.9 (1.3)	31.9 (1.9)	• OwnCig >NoNic = NicFreebase = NicSalt
PANAS Negative Affect	2.9	12.2 (0.6)	13.4 (0.6)	13.8 (1.1)	11.4 (0.8)	• NoNic = NicFreebase = NicSalt = OwnCig
Questionnaire of Smoking Urges						
Factor 1	23.0***	3.2 (0.1)	3.0 (0.2)	3.0 (0.2)	2.0 (0.3)	• OwnCig > NoNic = NicFreebase = NicSalt
Factor 2	18.3***	2.0 (0.1)	1.6 (0.2)	1.7 (0.1)	1.1 (0.2)	• OwnCig > NoNic = NicSalt = NicFreebase • NoNic > NicFreebase = NicSalt
Tobacco Product Evaluation Scale[‡]						
Satisfaction	37.2***	45.8 (5.5)	44.3 (5.0)	42.2 (5.1)	75.5 (4.8)	• OwnCig > NoNic = NicFreebase = NicSalt
Psychological Reward	25.2***	33.8 (5.2)	39.1 (5.0)	33.1 (4.9)	59.0 (4.3)	• OwnCig > NoNic = NicFreebase = NicSalt
Aversion	18.8***	13.7 (3.1)	31.2 (6.0)	31.4 (5.2)	35.0 (5.2)	• NoNic >NicFreebase = NicSalt = OwnCig
Sensory Enjoyment	19.9***	39.3 (6.4)	30.3 (5.2)	37.2 (5.5)	65.0 (6.3)	• OwnCig > NoNic = NicFreebase = NicSalt • NoNic > NicFreebase = NicSalt
Cigarette Craving Reduction	44.5***	27.8 (5.5)	37.0 (6.5)	36.8 (6.0)	73.5 (4.7)	• OwnCig > NoNic = NicFreebase = NicSalt
E-Cig Sensory Attributes[‡]						
Sweetness	4.5	68.6 (3.6)	61.0 (5.0)	57.1 (5.4)	N/A	• NoNic = NicFreebase = NicSalt = OwnCig
Smoothness	22.6***	67.5 (4.4)	38.8 (5.8)	45.6 (6.4)	N/A	• NoNic > NicFreebase = NicSalt
Bitterness	0.1	29.1 (4.7)	30.5 (4.4)	29.3 (5.3)	N/A	• NoNic = NicFreebase = NicSalt = OwnCig
Harshness	51.3***	23.3 (4.0)	57.3 (6.5)	54.8 (6.3)	N/A	• NoNic < NicFreebase = NicSalt
Physiological Assessments						
Heart rate, BPM[f]	14.1**	68.0 (1.2)	75.2 (1.6)	72.5 (1.2)	74.0 (2.0)	• NoNic > NicFreebase = NicSalt = OwnCig
Plasma Nicotine, ng/ml[§]	108.5***	0.7 (0.2)	2.7 (0.7)	1.6 (0.4)	10.9 (0.9)	• OwnCig > NicFreebase > NicSalt > NoNic
Behavioral Smoking Task						
Latency to smoking, min	8.4*	19.9 (4.9)	21.2 (4.7)	24.3 (4.8)	28.9 (4.6)	• OwnCig > NoNic = NicFreebase = NicSalt
Total no. cigarettes smoked	1.3	2.0 (0.3)	2.0 (0.4)	1.9 (0.3)	1.8 (0.3)	• NoNic = NicFreebase = NicSalt = OwnCig

Note. n = 24 (no. observations in each condition range from 20 to 24 across variables). Results from generalized estimated equation models adjusting for pre-product exposure value. Abbreviations: NoNic: E-cigarette with 0% nicotine solution. NicFreebase: E-cigarettes with 0.5% nicotine freebase solution. NicSalt: E-cigarette with 2.8% nicotine salt. PANAS: Positive Affect Negative Affect Schedule. Factor 1: intention to smoke and desire to smoke for pleasure. Factor 2: urge to smoke to alleviate negative affect.

† Chi-square omnibus test of omnibus group differences:

* P < 0.05;

** P < 0.01,

*** P < 0.001.

‡ Assessed only at post-product exposure.

§ n=22 (no. observations in each condition range from 18 to 20 due to missing data).

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