Title

Twenty-four-hour subjective and pharmacological effects of ad-libitum electronic and combustible cigarette use among dual users

Journal

Addiction, 115(6)

ISSN

0965-2140

Authors

Harvanko, Arit M

St Helen, Gideon

Nardone, Natalie

et al.

Publication Date

2020-06-01

DOI

10.1111/add.14931

Peer reviewed

HHS Public Access

Author manuscript

Addiction. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Addiction. 2020 June ; 115(6): 1149–1159. doi:10.1111/add.14931.

Twenty-four Hour Subjective and Pharmacological Effects of Ad Libitum Electronic and Combustible Cigarette Use among Dual Users

Arit M. Harvanko, PhD[1], **Gideon St. Helen, PhD**[1,2], **Natalie Nardone, PhD**[2], **Newton Addo**[2], **Neal L. Benowitz, MD**[1,2,3]

[1]Center for Tobacco Control Research and Education, University of California, San Francisco, California

[2]Clinical Pharmacology Research Program, Division of Cardiology, Zuckerberg San Francisco General Hospital, Department of Medicine, University of California, San Francisco, California

[3]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, California

Abstract

Background and Aims: Relative pharmacological effects of e-cigarettes and cigarettes over 24 h of *ad libitum* use have not been described. In this study 24 h blood plasma nicotine concentrations and 48 h subjective effects with use of cigarettes and e-cigarettes were measured among dual users.

Design: Two-arm within-subject crossover design with preferred e-cigarette or cigarette *ad libitum* use over 48 h.

Setting: Hospital research ward in San Francisco, California, USA.

Participants: 36 healthy dual users of e-cigarettes and cigarettes (N=8, 25% females).

Measurements: 24 h blood plasma nicotine and cotinine concentrations and 48 h self-reported nicotine withdrawal symptoms and rewarding effects.

Findings: Analyses used ANOVA based mixed models with order of product (e-cigarette or cigarette) and product type (combustible cigarette or type of e-cigarette) as fixed effects, and subject as a repeated effect. Over a 24 h period, e-cigarettes produced lower nicotine exposure than cigarettes for the majority of users, though 25% received more nicotine from e-cigarettes – which was predicted by more frequent e-cigarette use or greater dependence. Compared to cigarette smoking, nicotine exposure for variable-power tank users was similar, while cig-a-like (t[30]=2.71, p=.011, d=.745) and fixed-power tank users (t[30]=3.37, p=.002, d=.993) were exposed to less nicotine. Cigarettes were rated higher than e-cigarettes on some desirable

Correspondence concerning this article should be addressed to: Neal L. Benowitz MD, University of California San Francisco, Box 1220, San Francisco, CA 94143-1220. Phone: 415-206-8324; Fax: 415-206-4956; Neal.Benowitz@ucsf.edu.

Declarations of competing interest: Dr. Benowitz is a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications. He has also been a paid expert witness in litigation against tobacco companies.

ClinicalTrials.gov **Identifier:** NCT02470754

subjective effects (e.g. psychological reward, t[322]=7.24 $p<.001$, $d=.432$)), but withdrawal symptom reduction was comparable. No differences were found between e-cigarette types but Bayes factors indicate these measures were insensitive.

Conclusions: Across a 24h-period in a hospital setting in the US, nicotine exposure for dual users of e-cigarettes and cigarettes was similar when using cigarettes or variable-power tank devices only but was lower for those using cig-a-like or fixed power devices only. Despite lower nicotine levels, all types of e-cigarette were effective in preventing withdrawal symptoms. E-cigarettes were rated less rewarding than cigarettes.

Keywords

behavior; nicotine; e-cigarettes; ENDS; blood; plasma; area under the curve; smoking; vaping

INTRODUCTION

Termed “dual use,” many individuals report concurrent use of electronic cigarettes (e-cigarettes) and combustible cigarettes (cigarettes) (1, 2). Dual use could attenuate harm by reducing use of cigarettes with partial substitution of nicotine from e-cigarettes (3, 4), or increase harm by delaying quitting cigarettes (5) and increasing cumulative exposure to tobacco toxicants (6). Recent data suggest that for many, dual use is not a path towards cigarette quitting (2, 4). For example, though most report using e-cigarettes for smoking cessation (7, 9), 88% of dual users have continued dual-use (44.3%) or cigarette only use (43.5%) over one year in one study (2).

To gain insight into dual use, our study addressed the following questions: among dual users of e-cigarettes and cigarettes, comparing use of products used exclusively over a 24 h period, 1) do e-cigarettes and cigarettes produce similar nicotine levels, 2) does e-cigarette type play a significant role in nicotine exposure, 3) over a 48 h period do e-cigarettes and cigarettes produce comparable subjective reward and attenuation of withdrawal symptoms, and 4) do e-cigarette sub-types produce comparable subjective reward and attenuation of tobacco withdrawal symptoms?

Some e-cigarettes are *capable* of delivering nicotine nearly as rapidly, and in comparable amounts, as cigarettes (10–12). However, e-cigarettes have demonstrated variability in nicotine delivery (11, 13, 14). Nicotine exposure studies typically incorporate single use sessions with fixed puffing bouts or short-term *ad libitum* procedures. Plasma nicotine concentrations are typically higher from *ad libitum* use compared to fixed puffing (12, 15–17), perhaps because *ad libitum* procedures allow e-cigarette users to self-administer aerosols to achieve desired nicotine levels. However, *ad libitum* periods used in pharmacokinetic studies are typically brief (5-115 minutes) (13).

Characteristics of e-cigarettes influence their ability to delivery nicotine (18–20). But, e-cigarette users can make compensatory changes (e.g. puff frequency, duration, or volume) to achieve desired levels of nicotine in the body (16, 20–22). It is unknown, however, how nicotine exposure differs with device type during *ad libitum* use throughout the day.

Stimulus characteristics influence subjective effects of cigarettes (23) and e-cigarettes (24). Similar to denicotinized cigarettes (25), e-cigarettes without nicotine can reduce tobacco withdrawal symptoms, but less than nicotine containing e-cigarettes (26). However, e-cigarettes containing nicotine are reported not to reduce withdrawal symptoms as much as cigarettes (26, 27) – perhaps because nicotine delivery is not the only factor in managing cigarette withdrawal symptoms. Differences between e-cigarette types can affect stimulus characteristics. For example, cig-a-likes provide visual and tactile experiences more similar to cigarettes, which can affect cigarette withdrawal symptom management (28). Sensation of puffs in the mouth and throat differ by e-cigarette type (29), with some delivering sensations more comparable to cigarettes (15). To understand the mechanisms underlying rewarding effects of e-cigarettes and ability to manage cigarette withdrawal symptoms, it is important to examine nicotine exposure (i.e. plasma nicotine concentration) and subjective effects (e.g. withdrawal symptom alleviation and rewarding effects).

E-cigarette nicotine exposure has been measured during shorter periods (< 2 h) in laboratory settings, and subjective effects during longer periods outside of the laboratory (30), but we are unaware of a laboratory study looking at both over 24 h. Compared to shorter *ad libitum* usage periods, 24 h use is likely more comparable to the natural environment. To address aforementioned research questions a two-arm within-subject crossover clinical study compared 24 h nicotine exposure and 48 h subjective effects of own brand e-cigarette or cigarette; and a secondary analysis assessed differences between-participants with different e-cigarette types.

METHODS

Participants

Thirty-six dual users (25% [*N*=8] females), who used an e-cigarette at least 15 days of the past 30, and smoked at least 5 cigarettes/day for the past 30 days, were recruited via newspapers and the Internet. To enhance the likelihood that participants were smoking/vaping for pharmacologic effects of nicotine, clinically significant nicotine intake was confirmed by salivary cotinine levels of ≥ 50 ng/mL. Exclusion criteria included: use of e-cigarette liquids < 6 mg/mL nicotine concentration, < 21 years of age, intent to quit e-cigarettes or cigarettes over the next 3 months, pregnancy, use of nicotine metabolism-altering medications, chronic medical diseases and active substance dependence or recent use of drugs of abuse other than marijuana. The study was approved by the Institutional Review Board at the University of California San Francisco. Written, informed consent was obtained from participants and they were financially compensated.

General Procedures

Screening occurred at an outpatient research clinic where consent was obtained, questionnaires completed, and saliva collected for cotinine measurement. Participants were not asked to modify their smoking or e-cigarette use behavior prior to screening. After screening, all eligible participants completed two one-week blocks – one cigarette and one e-cigarette block – in a counterbalanced order. The first four days of each block consisted of at home use of e-cigarettes or cigarettes (data to be presented in another manuscript), which

also served as a wash out period between in-hospital sessions. On the fifth day, fixed-administration of the products was assessed on a hospital ward (31), and the sixth and seventh days (hereafter referred to as the 'first' and 'second' days) consisted of *ad libitum* use of e-cigarettes or cigarettes while subjective effects were assessed over the entire 48 h period, and blood specimens collected over the second 24 h period. Only results from the two in-hospital *ad libitum* study days of each block are presented in this report.

On *ad libitum* days, participants were provided with their own brand cigarette or e-cigarette with slightly more than their normal supply to account for use of only one product at a time. No participants ran out of e-cigarette liquids or cigarettes during the course of the day. While on the hospital ward participants were in their own private room, allowed access to television, reading materials of their choice, Internet, and to go on supervised walks with study staff.

At 8:00 A.M. on the first day, following 8 h of abstinence, participants were free to use their e-cigarette (at preferred power levels for variable-power devices) or cigarettes *ad libitum* until midnight. Subjective effects questionnaires were administered prior to product use at 8:00 A.M., following initial product usage at 8:15 A.M., and noon, 4:00 P.M., and 8:00 P.M. Second day procedures were identical to the first day with the addition of blood samples taken via intravenous catheter every four hours from 8:00 A.M.-midnight, and at 8:00 A.M. the following day.

Device categorization—Devices were categorized into four groups consistent with previous research (32, 33), 1) 'cig-a-likes': small cylindrical devices resembling combustible cigarettes with non-refillable liquid cartridges, 2) 'fixed-power tanks': devices with refillable tanks and no user-adjustable power parameters, 3) 'variable-power tanks': similar to fixed-power devices but with the ability to change power parameters (e.g. voltage or wattage), and 4) 'pods': devices utilizing disposable pods with nicotine salt liquids.

Assessments

Nicotine and Cotinine Measures—Plasma nicotine and cotinine concentrations, salivary cotinine concentrations at screening, and nicotine concentrations in participants' EC liquids, were determined by gas chromatography – tandem mass spectrometry/mass spectrometry (34). The limit of quantitation (LOQ) for salivary cotinine was 10 ng/mL, and all others was 0.2 ng/mL.

Questionnaires—At screening, participants completed a basic demographic questionnaire including their age, sex, and race, and a nicotine use history questionnaire on past 30-day cigarette and e-cigarette use, e-cigarette type used most, typical nicotine concentration (in mg/mL), and mL of e-cigarette liquid per week.

Fagerstrom Test for Cigarette Dependence (FTCD; 35)—This six-item self-report scale assesses cigarette dependence, with higher scores indicating greater dependence. The total score is the outcome variable for this measure. This scale was administered at the screening visit.

Penn State [Electronic] Cigarette Dependence Index (PSCDI; 36)—This ten-item self-report scale assesses e-cigarette dependence, with higher scores indicating greater dependence. The total score is the outcome variable for this measure. This scale was administered at the screening visit.

Questionnaire of Smoking Urges (QSU; 37)—This 10-item self-report scale uses a seven-point Likert to assess two-factors associated with reward or relief from withdrawal symptoms associated with e-cigarette or cigarettes: Factor 1 ‘desire and intention to smoke,’ and Factor 2 ‘relief from negative affect by smoking.’ Outcome variables included scores for each of the two factors. Both an e-cigarette and cigarette version of this scale were given whenever subjective effects scales were administered.

Modified Cigarette Evaluation Questionnaire (mCEQ; 38)—This 12-item self-report scale uses a seven-point Likert response format to assess five factors. Three factors are associated with reward (‘smoking satisfaction,’ ‘psychological reward,’ ‘enjoyment of respiratory tract sensations’), one factor is associated with withdrawal symptoms (‘craving reduction’), and the fifth factor is related to undesirable effects of nicotine (‘aversion’). Outcome variables include scores for each of the five factors. This scale was administered whenever subjective effects scales were administered.

Positive and Negative Affect Scale (PANAS; 39)—This 10-item self-report scale uses a five-point Likert scale to assess positive and negative feelings and emotions. This scale was included based on evidence that nicotine boost is associated with positive mood (40). Outcome variables included scores on the positive or negative factors. This scale was administered at all but the 8:15 A.M. time points.

Minnesota Nicotine Withdrawal Scale (MNWS; 41)—This 15-item self-report scale uses a five-point Likert scale to assess nicotine withdrawal symptoms. Total scores are the outcome variable on this measure. This scale was administered at all but the 8:15 A.M. time points.

Statistical Analysis

A priori sample size calculations determined a power of 86% with alpha = .05 would be achieved for differences between e-cigarettes and cigarettes assuming a 1.2 ratio of differences and 25% coefficient of variation based on previous research examining plasma cotinine in smokers (42). Sample size calculations were not conducted for the secondary analyses of differences between e-cigarette types. Area-under-the-curve values for plasma nicotine and cotinine concentrations over time (AUC) were calculated using the trapezoidal rule. Differences between cigarettes and e-cigarettes were tested using ANOVA based mixed models with compound symmetry covariance structure, order of product (e-cigarette or cigarette) and product type were input as fixed effects, and subject as a repeated effect. The compound symmetry covariance structure was selected to reflect the counterbalanced and symmetrical design of the two arms of the study.

Nicotine titration between e-cigarettes and cigarettes was calculated by $\frac{e-cigarette}{cigarette}$ area under the 24 h plasma nicotine concentration-time curve values, such that < 1 indicates less exposure, one indicates equal exposure, and > 1 equals greater exposure from e-cigarettes compared to cigarettes. A variable representing 'average daily use of e-cigarettes compared to cigarettes' over the past 30 days was calculated as: $\frac{(e-cigarette\ times\ per\ day)\times(e-cigarette\ using\ days\ per\ month)}{\text{cigarettes per day}}$ (31). For individuals using refillable type e-cigarettes, 'nicotine used per week' was calculated as self-reported mL's of e-cigarette liquid used per day multiplied by seven and the percentage of nicotine concentration typically used. Pearson's correlations were used to compare relationships between nicotine titration and other e-cigarette or cigarette use variables. To examine whether level of nicotine exposure from cigarettes was associated with nicotine exposure from e-cigarettes — plasma nicotine AUC from e-cigarettes was subtracted from within-subject plasma nicotine AUC from cigarettes to test for a correlation with e-cigarette plasma nicotine AUC. Because only three (8.3%) participants used a pod type e-cigarette, these participants were excluded from device sub-type analyses due to lack of statistical power for this group.

Subjective effects from cigarettes and e-cigarettes was tested using ANOVA based mixed models with compound symmetry covariance structure and order of product and product type as fixed effects, and time as a random effect. Secondary analysis of subjective effects and plasma nicotine and cotinine levels between e-cigarette types was conducted using ANOVA based mixed models with variance components covariance structure and order of product, time, e-cigarette or cigarette, and e-cigarette type as a fixed effect, and subject as a repeated effect (nicotine and cotinine models) or intercept as a random effects (subjective effects models). When main effects were indicated, t-tests for differences in least-squares means from the mixed model were conducted and multiple-comparisons adjusted using Hochberg's step-up procedure (43). Effect sizes for fixed effects in mixed models are reported as Cohen's f^2 calculated using a previously described method (44) and effect sizes for post-hoc t-tests are reported as Cohen's *d*. When product type comparison was not significant, a Bayes factor was calculated (45). Scatter plots for correlations and residual plots for mixed models were examined for homogeneity of variance and normality. Analyses were conducted using SAS v. 9.4 (SAS Institute, Inc., Cary, NC, USA) and $\alpha<0.05$. This analysis plan was not pre-registered and the results should be considered exploratory.

RESULTS

Descriptive statistics of demographic and e-cigarette and cigarette use variables are presented in Table 1.

Comparison of plasma nicotine levels with use of e-cigarettes and cigarettes

Temporal patterns of e-cigarette and cigarette plasma concentrations were similar for nicotine and cotinine (Figure 1). Product type had an effect on plasma nicotine AUC ($F[1,35]=8.67$, $p=.006$, $f^2=.213$) and plasma cotinine AUC ($F[1,35]=8.19$, $p=.007$, $f^2=.200$) with cigarettes being associated with higher levels compared to e-cigarettes. Product order

did not have an effect on nicotine AUC (F[1,34]=0.78, p=.385, f^2< .001) or cotinine AUC (F[1,34]=0.53, p=.470, f^2< .001).

Individual differences in plasma nicotine AUC for e-cigarettes and cigarettes are shown in Figure 2A and nicotine titration values in Figure 2B. Extent of nicotine titration was positively correlated with three screening variables (Table 2): 1) average number of times e-cigarettes were used per day in the past 30 days (r[36]=.49, p=.003), 2) PSCDI total score (r[36]=.50, p=.002), and 3) average daily use of e-cigarettes compared to cigarettes (r[36]=.56, p<.001) (Figure 3). A correlation was found between 'cigarette minus e-cigarette plasma nicotine AUC' and 'cigarette plasma nicotine AUC' (r[36]=51, p=.002) (Supplementary Figure 2).

E-cigarette type and 24 h plasma nicotine concentrations

Among e-cigarette types and cigarettes, there was a main effect for plasma nicotine AUC (F[3,30]=6.18, p=.002, f^2=.36) and no effect of product order (F[1,31]=.43, p=.515, f^2< .001). Variable-power tank e-cigarettes produced higher nicotine AUC (m=412.81 SE=65.94) compared to cig-a-like (m=208.78 SE=47.28) (t[30]=2.53, p=.017, d=1.212) and fixed-power tank devices (m=190.04 SE=42.02) (t[30]=2.87, p=.008, d=1.372) (Figure 4). Compared to cigarettes (m=348.63 SE=28.81), cig-a-like and fixed-power tanks were associated with lower nicotine AUC (p's <.02). Patterns of nicotine exposure between cigarettes and e-cigarettes among pod type (JUUL) users were visually similar (Supplementary Figure 1).

Comparison of subjective effects with use of e-cigarettes and cigarettes

Results of subjective effects analysis between e-cigarettes and cigarettes are displayed in Table 3. Cigarettes were rated higher than e-cigarettes on all five mCEQ subscales. E-cigarettes were rated higher than cigarettes on both factors of the e-cigarette version of the QSU. There was no effect between cigarette and e-cigarette on the MNWS or PANAS (all Bayes factors < 0.12)

Comparison of subjective effects between e-cigarette sub-types

Results of subjective effects analyses between e-cigarettes types are displayed in Table 4. We did not detect a significant effect of e-cigarette type on any of the subjective effects examined here, but all Bayes factors were within the pre-established range (1/3 to 3) that indicates the data are "insensitive" (45).

DISCUSSION

To the best of our knowledge, this is the first study of 24 h nicotine exposure and 48 h subjective effects comparing *ad libitum* cigarette and e-cigarette use among dual users. With preferred e-cigarette device, liquid flavor, nicotine concentration, and device settings, 24 h nicotine exposure with use of e-cigarettes and cigarettes was consistent with previous research on cigarettes (46), with a rapid rise early in the day and maximum levels towards the end of the day (e.g. midnight) (Figure 1).

Although most participants had greater nicotine exposure from cigarettes, 25% attained higher exposure from e-cigarettes (Figure 2). Greater nicotine exposure from cigarettes compared to e-cigarettes is consistent with findings from fixed-puffing (11, 47) or shorter *ad libitum* use periods (47, 48). History of relatively greater e-cigarettes use compared to cigarettes, frequency of e-cigarette use per day, and level of dependence on e-cigarettes were associated with more complete nicotine titration from e-cigarettes. Also, those who obtained more nicotine from cigarettes had a greater disparity between combustible cigarette and e-cigarette nicotine exposure, suggesting e-cigarettes provide insufficient nicotine to satisfy heavier smokers.

Variable-power tank devices produced nicotine exposure comparable to cigarettes and greater than fixed-power tank and cig-a-like devices (Figure 4). The three pod (Juul) users had similar temporal patterns of nicotine exposure between their cigarette and e-cigarette (Supplementary Figure 1), although these data were not evaluated with inferential statistics. Our results are consistent with previous findings that smaller and less powerful e-cigarettes (i.e. cig-a-likes) typically deliver less nicotine than other e-cigarettes over five minutes (48) or 1 h of *ad libitum* use (15), although two cig-a-like users (17% of cig-a-like users) were exposed to more nicotine from e-cigarettes than from cigarettes.

Greater nicotine exposure from variable-power devices relative to fixed-power devices is consistent with research using similarly categorized devices and a 2 h *ad libitum* usage period (12), perhaps because individuals who use adjustable e-cigarettes set them to higher wattages than non-adjustable devices. Indeed, of participants whose device power could be ascertained, variable-power devices were set to higher wattages (N=5 [83.3%], m=39.4 watts, SD=29.3) than fixed-power devices (N=10 [63.3%], m=10.0 watts, SD=6.4).

With all else equal, greater e-cigarette power level should lead to greater nicotine exposure. However, greater power is typically associated with use of lower nicotine concentration liquids, suggesting users balance device settings to regulate overall nicotine delivery (9). Results of our study suggest these changes are not fully compensatory and nicotine exposure is still greater from the higher powered variable-power devices. Because variable power devices are associated with greater nicotine exposure, and e-cigarette only users are more likely to use variable-power e-cigarettes (49), greater nicotine exposure is likely important for smoking cessation. This idea is supported by the fact that cig-a-like users are more likely to return to cigarettes compared to variable-power device users (50, 51).

Consistent with greater nicotine exposure, cigarettes were associated with greater rewarding effects (i.e. mCEQ respiratory tract sensations and psychological reward subscales) and some undesirable effects (i.e. ‘dizziness’ and ‘nausea’ items comprising the ‘aversion’ subscale of the mCEQ) relative to e-cigarettes. Similarly, other research has shown rewarding subjective effects are greater from cigarettes relative to e-cigarettes following *ad libitum* use (27), and in qualitative interviews (52). Although nicotine exposure was greater from cigarettes - there was no difference in overall withdrawal symptoms measured by the MNWS. Cigarettes did, however, reduce the specific withdrawal symptom ‘craving reduction’ (measured by the mCEQ) more than e-cigarettes. These findings are consistent with past studies showing e-cigarettes are capable of alleviating cigarette withdrawal

symptoms following *ad libitum* use (53, 54). Overall, our data show that e-cigarettes produce less desirable effects than cigarettes but comparably manage overall withdrawal symptoms. Less rewarding effects from e-cigarettes relative to cigarettes may be why many dual users fail to completely switch to e-cigarettes.

Comparing e-cigarette device types, there were no differences in the subjective effects examined here, though Bayes factors indicate these measures were insensitive. This indicates that if there are differences in subjective effects between e-cigarette types, the effects were not large enough to be reliably measured in this study, perhaps because participants in this study self-selected their devices to achieve optimal subjective effects (29).

In conclusion, in dual users cigarette smoking alone generally produces greater daily nicotine exposure than e-cigarette use alone, although patterns of nicotine levels are similar over a 24 h period of *ad libitum* use. However, 25% of participants were exposed to more nicotine when using e-cigarettes. Participants who are exposed to more nicotine from cigarettes were less likely to attain comparable levels from e-cigarettes. E-cigarette type, liquid nicotine concentration, and cigarette use variables were not predictive of nicotine titration; most predictive were greater e-cigarette dependence and greater relative use of e-cigarettes during the 30 days prior to study participation. Those using cig-a-like devices and fixed-power tank devices were exposed to less nicotine than from cigarettes. From a smoking cessation perspective, devices producing nicotine exposure comparable to cigarettes — such as variable-power tank e-cigarettes — may be more effective than other device types. Although, e-cigarettes associated with less nicotine exposure than cigarettes may still be effective at preventing withdrawal symptoms.

Limitations

Dual users were recruited to study the independent effects of cigarettes and e-cigarettes in experienced users but were limited to one product at a time during the study, which may have affected natural usage patterns. Similarly, participants were restricted to only their preferred type and brand of each throughout the study, while they may use multiple types or brands of e-cigarettes and cigarettes in daily life. Although participants were allowed to use their preferred products *ad libitum* throughout two days, we were not able to simulate every aspect of normal life within the hospital ward. Type of e-cigarette was not experimentally controlled and participants self-selected e-cigarette types based on individual preferences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: The research reported in this publication was supported by the National Institute on Drug Abuse (R01DA039264-03) and the National Cancer Institute (T32CA113710), of the National Institute of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Prevalence and correlates of current daily use of electronic cigarettes in the European Union: analysis of the 2014 Eurobarometer survey. Intern Emerg Med. 2017;12(6):757–763. [PubMed: 28260221]
2. Coleman B, Rostron B, Johnson SE, et al. Transitions in electronic cigarette use among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 1 and 2 (2013–2015). Tob Control. 2019;28(1):50–59. [PubMed: 29695458]
3. McRobbie H, Phillips A, Goniewicz ML, et al. Effects of switching to electronic cigarettes with and without concurrent smoking on exposure to nicotine, carbon monoxide, and acrolein. Cancer Prev Res (Phila). 2015;8(9):873–878. [PubMed: 26333731]
4. Piper ME, Baker TB, Benowitz NL, Kobinsky KH, Jorenby DE, Research T. Dual users compared to smokers: demographics, dependence, and biomarkers. Nicotine Tob Res.2018;21(9):1279–1284.
5. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. The Lancet Respiratory Medicine. 2016;4(2):116–128. [PubMed: 26776875]
6. Goniewicz ML, Smith DM, Edwards KC, et al. Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. JAMA Netw Open. 2018;1(8):e185937. [PubMed: 30646298]
7. Li J, Newcombe R, Walton D. The prevalence, correlates and reasons for using electronic cigarettes among New Zealand adults. Addict behav. 2015;45:245–251. [PubMed: 25744712]
8. Ayers JW, Leas EC, Allem JP, et al. Why do people use electronic nicotine delivery systems (electronic cigarettes)? A content analysis of Twitter, 2012–2015. PloS one. 2017;12(3):e0170702. [PubMed: 28248987]
9. Harvanko AM, McCubbin AK, Ashford KB, Kelly TH. Electronic cigarette liquid and device parameters and aerosol characteristics: A survey of regular users. Addict Behav. 2018;84:201–206. [PubMed: 29723803]
10. Ramoa CP, Hiler MM, Spindle TR, et al. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. Tob Control. 2016;25(e1):e6–9. [PubMed: 26324250]
11. St Helen G, Havel C, Dempsey DA, Jacob P 3rd, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction. 2016;111(3):535–544. [PubMed: 26430813]
12. Wagener TL, Floyd EL, Stepanov I, et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tob Control. 2017;26(e1):e23–e28. [PubMed: 27729564]
13. Fearon IM, Eldridge AC, Gale N, McEwan M, Stiles MF, Round EK. Nicotine pharmacokinetics of electronic cigarettes: A review of the literature. Regul Toxicol Pharmacol. 2018;100:25–34. [PubMed: 30201538]
14. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. Nicotine Tob Res. 2013;15(1):267–270. [PubMed: 22311962]
15. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. Sci Rep. 2014;4:4133. [PubMed: 24569565]
16. Farsalinos KE, Voudris V, Spyrou A, Poulas K. E-cigarettes emit very high formaldehyde levels only in conditions that are aversive to users: A replication study under verified realistic use conditions. Food Chem Toxicol. 2017;109(Pt 1):90–94. [PubMed: 28864295]
17. St Helen G, Dempsey DA, Havel CM, Jacob P 3rd, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. Drug Alcohol Depend. 2017;178:391–398. [PubMed: 28704768]
18. DeVito EE, Krishnan-Sarin S. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. Curr Neuropharmacol. 2018;16(4):438–459. [PubMed: 29046158]
19. Stratton KR, Kwan LY, Eaton DL, National Academies of Sciences Engineering and Medicine (U.S.). Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems

Public health consequences of e-cigarettes. Washington, DC: The National Academies Press; 2018.

20. Lopez AA, Hiler MM, Soule EK, et al. Effects of Electronic Cigarette Liquid Nicotine Concentration on Plasma Nicotine and Puff Topography in Tobacco Cigarette Smokers: A Preliminary Report. Nicotine Tob Res. 2016;18(5):720–723. [PubMed: 26377515]
21. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine Tob Res. 2015;17(2):158–162. [PubMed: 25180079]
22. Kosmider L, Spindle TR, Gawron M, Sobczak A, Goniewicz ML. Nicotine emissions from electronic cigarettes: Individual and interactive effects of propylene glycol to vegetable glycerin composition and device power output. Food Chem Toxicol. 2018;115:302–305. [PubMed: 29572013]
23. Rose JE. Nicotine and nonnicotine factors in cigarette addiction. Psychopharmacology (Berl). 2006;184(3-4):274–285. [PubMed: 16362402]
24. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control. 2010;19(2):98–103. [PubMed: 20378585]
25. Rose JE, Behm FM, Westman EC, Johnson M. Dissociating nicotine and nonnicotine components of cigarette smoking. Pharmacol Biochem Behav. 2000;67(1):71–81. [PubMed: 11113486]
26. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction. 2012;107(8):1493–1500. [PubMed: 22229871]
27. Stiles MF, Campbell LR, Jin T, Graff DW, Fant RV, Henningfield JE. Assessment of the abuse liability of three menthol Vuse Solo electronic cigarettes relative to combustible cigarettes and nicotine gum. Psychopharmacology (Berl). 2018;235(7):2077–2086. [PubMed: 29725702]
28. Dawkins L, Munafò M, Christoforou G, Olumegbon N, Soar K. The effects of e-cigarette visual appearance on craving and withdrawal symptoms in abstinent smokers. Psychol *Addict Behav*. 2016;30(1):101. [PubMed: 26415054]
29. Hajek P, Przulj D, Phillips-Waller A, Anderson R, McRobbie H. Initial ratings of different types of e-cigarettes and relationships between product appeal and nicotine delivery. Psychopharmacology (Berl). 2018;235(4):1083–1092. [PubMed: 29306962]
30. Robinson RJ, Hensel EC, Al-Olayan AA, Nonnemaker JM, Lee YO. Effect of e-liquid flavor on electronic cigarette topography and consumption behavior in a 2-week natural environment switching study. PLoS One. 2018;13(5):e0196640. [PubMed: 29718974]
31. St.Helen G, Nardone N, Addo N, et al. Differences in nicotine intake and effects from electronic and combustible cigarettes among dual users. Addiction. 2019.
32. Malek N, Nakkash R, Talih S, et al. A Transdisciplinary Approach to Understanding Characteristics of Electronic Cigarettes. Tob Regul Sci. 2018;4(3):47–72.
33. Spindle TR, Talih S, Hiler MM, et al. Effects of electronic cigarette liquid solvents propylene glycol and vegetable glycerin on user nicotine delivery, heart rate, subjective effects, and puff topography. Drug Alcohol Depend. 2018;188:193–199. [PubMed: 29778773]
34. Jacob P 3rd, Yu L, Wilson M, Benowitz NL. Selected ion monitoring method for determination of nicotine, cotinine and deuterium-labeled analogs: absence of an isotope effect in the clearance of (S)-nicotine-3',3'-d2 in humans. Biol Mass Spectrom. 1991;20(5):247–252. [PubMed: 1883864]
35. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991;86(9):1119–1127. [PubMed: 1932883]
36. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. Nicotine Tob Res. 2015;17(2):186–192. [PubMed: 25332459]
37. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res. 2001;3(1):7–16. [PubMed: 11260806]
38. Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007;32(5):912–923. [PubMed: 16875787]

39. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988;54(6):1063–1070. [PubMed: 3397865]
40. Patterson F, Benowitz N, Shields P, et al. Individual differences in nicotine intake per cigarette. Cancer Epidemiol Biomark Prev. 2003;12(5):468–471.
41. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry. 1986;43(3):289–294. [PubMed: 3954551]
42. St Helen G, Novalen M, Heitjan DF, et al. Reproducibility of the nicotine metabolite ratio in cigarette smokers. Cancer Epidemiol Biomark Prev. 2012;21(7):1105–1114.
43. Hochberg Y A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):2.
44. Selya AS, Rose JS, Dierker LC, Hedeker D, Mermelstein RJ. A Practical Guide to Calculating Cohen's f(2), a Measure of Local Effect Size, from PROC MIXED. Front Psychol. 2012;3:111. [PubMed: 22529829]
45. Beard E, Dienes Z, Muirhead C, West R. Using Bayes factors for testing hypotheses about intervention effectiveness in addictions research. Addiction. 2016;111(12):2230–2247. [PubMed: 27347846]
46. Benowitz NL, Kuyt F, Jacob P 3rd. Circadian blood nicotine concentrations during cigarette smoking. Clin Pharmacol Ther. 1982;32(6):758–764. [PubMed: 7140139]
47. Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. Regul Toxicol Pharmacol. 2015;71(1):24–34. [PubMed: 25460033]
48. Hajek P, Przulj D, Phillips A, Anderson R, McRobbie H. Nicotine delivery to users from cigarettes and from different types of e-cigarettes. Psychopharmacology (Berl). 2017;234(5):773–779. [PubMed: 28070620]
49. Nardone N, Ko J St Helen G, Benowitz NL. Nicotine Intake, Dependence, and Characteristics of Electronic Cigarette and Dual Users. Tob Regul Sci.. 2019;5(1):27–35.
50. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. Nicotine Tob Res. 2015;17(10):1187–1194. [PubMed: 25896067]
51. Yingst J, Foulds J, Veldheer S, Du P. Device characteristics of long term electronic cigarette users: A follow-up study. Addict Behav. 2019 4;91:238–243. [PubMed: 30270024]
52. Jorenby DE, Smith SS, Fiore MC, Baker TB. Nicotine levels, withdrawal symptoms, and smoking reduction success in real world use: A comparison of cigarette smokers and dual users of both cigarettes and E-cigarettes. Drug Alcohol Depend. 2017;170:93–101. [PubMed: 27883949]
53. Kim H, Davis AH, Dohack JL, Clark PI. E-Cigarettes Use Behavior and Experience of Adults: Qualitative Research Findings to Inform E-Cigarette Use Measure Development. Nicotine Tob Res. 2017;19(2):190–196. [PubMed: 27613944]
54. Palmer AM, Brandon TH. How do electronic cigarettes affect cravings to smoke or vape? Parsing the influences of nicotine and expectancies using the balanced-placebo design. J Consult Clin Psychol. 2018;86(5):486–491. [PubMed: 29683704]

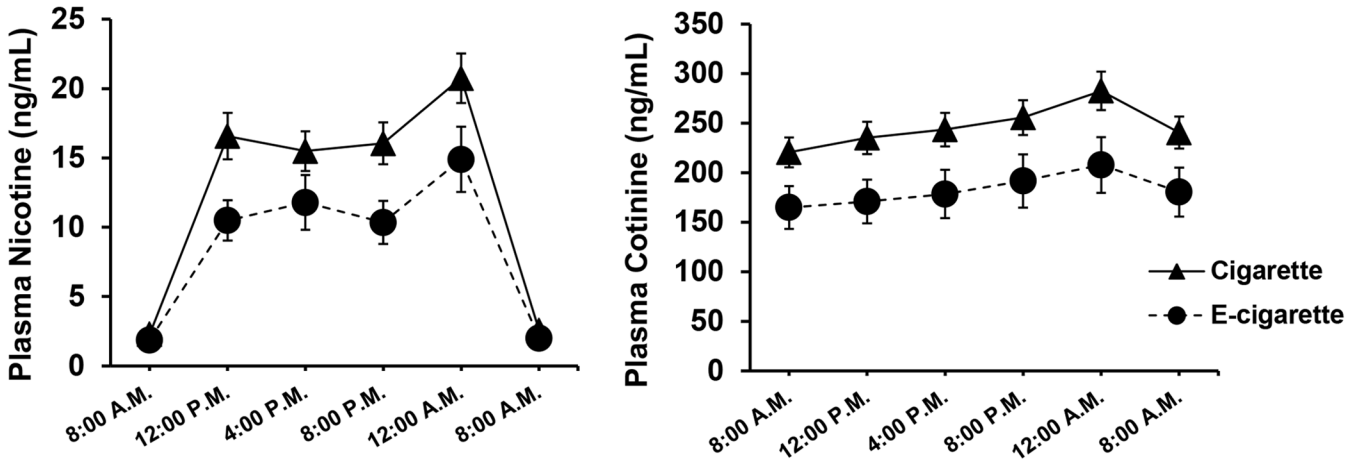

Figure 1. 24-hour Plasma Cotinine and Nicotine Levels

Points represent mean values with standard error bars. Higher plasma nicotine area-under-the-curve (F[1,35]=8.67, p=.006, f^2=0.21) was produced by cigarettes (m=334.11, SE=28.27) compared to e-cigarettes (m=231.86, SE=28.27). Higher plasma cotinine area-under-the-curve (F[1,35]=8.19, p=.007, f^2=0.20) was produced by cigarettes (m=6104.27, SE=521.32) compared to e-cigarettes (m=4505.45, SE=521.32).

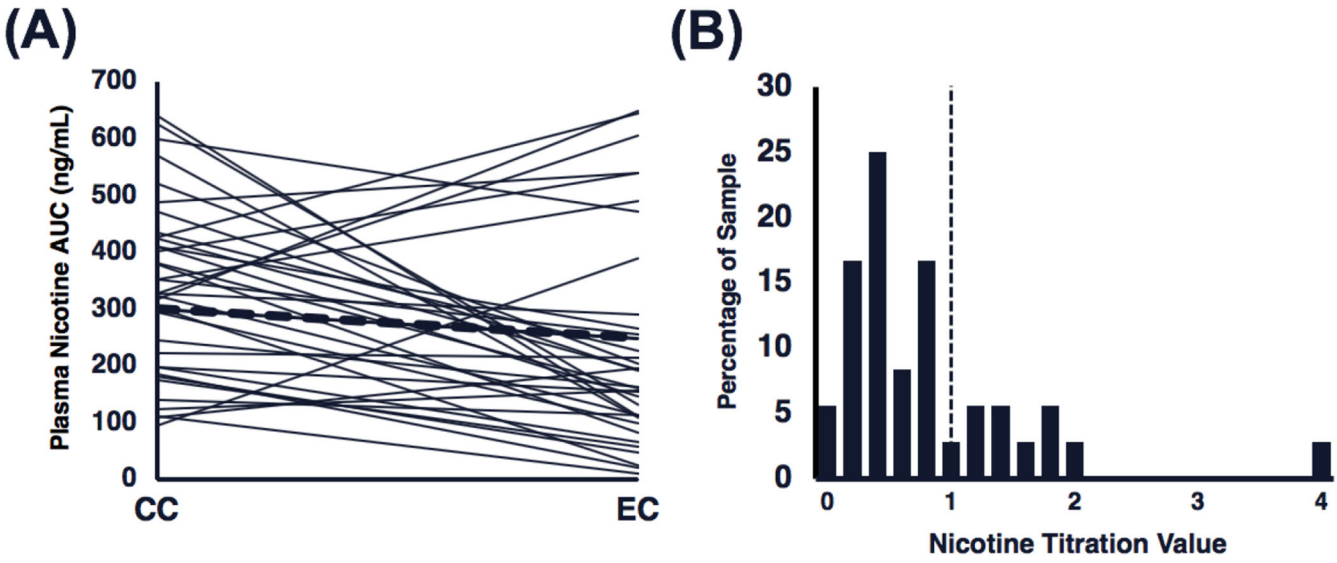

Figure 2. Individual Plasma Nicotine AUC Levels and Nicotine Titration Ratios

AUC = area under the curve; CC = combustible cigarette; EC = Electronic cigarette. Individual plasma nicotine AUC values with solid lines representing individual values and the dashed line representing average values (A). Nicotine titration ratios were calculated by $\frac{E-cigarette\ Plasma\ Nicotine\ AUC}{Cigarette\ Plasma\ Nicotine\ AUC}$ and represent the extent individuals titrated nicotine intake between e-cigarettes and cigarettes. The dashed line represents the point where equal nicotine levels were achieved from e-cigarette and cigarette (B).

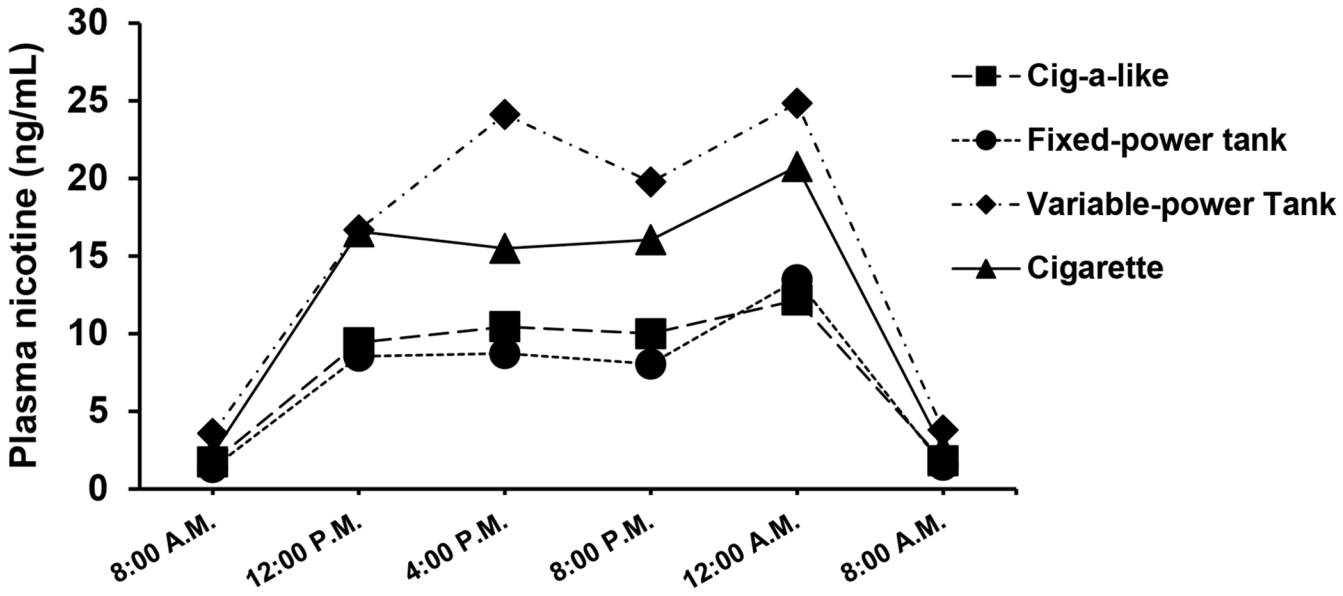

Figure 3. Plasma Nicotine Concentrations by Device Type

Points represent mean values for each device. Type of product had a main effect on plasma nicotine AUC ($F[30]=6.18$, $p=.002$, $f^2=.36$). Cigarettes produced higher plasma nicotine area-under-the-curve (AUC) compared to cig-a-like ($t[30]=2.71$, $p=.011$, $d= .745$) and fixed-power tank ($t[30]=3.37$, $p=.002$, $d= .993$) type e-cigarettes. Variable-power tank devices produced higher plasma nicotine AUC compared to cig-a-like ($t[30]=2.53$, $p=.017$, $d= 1.212$) and fixed-power tank ($t[30]=2.87$, $p=.008$, $d= 1.372$) types e-cigarettes.

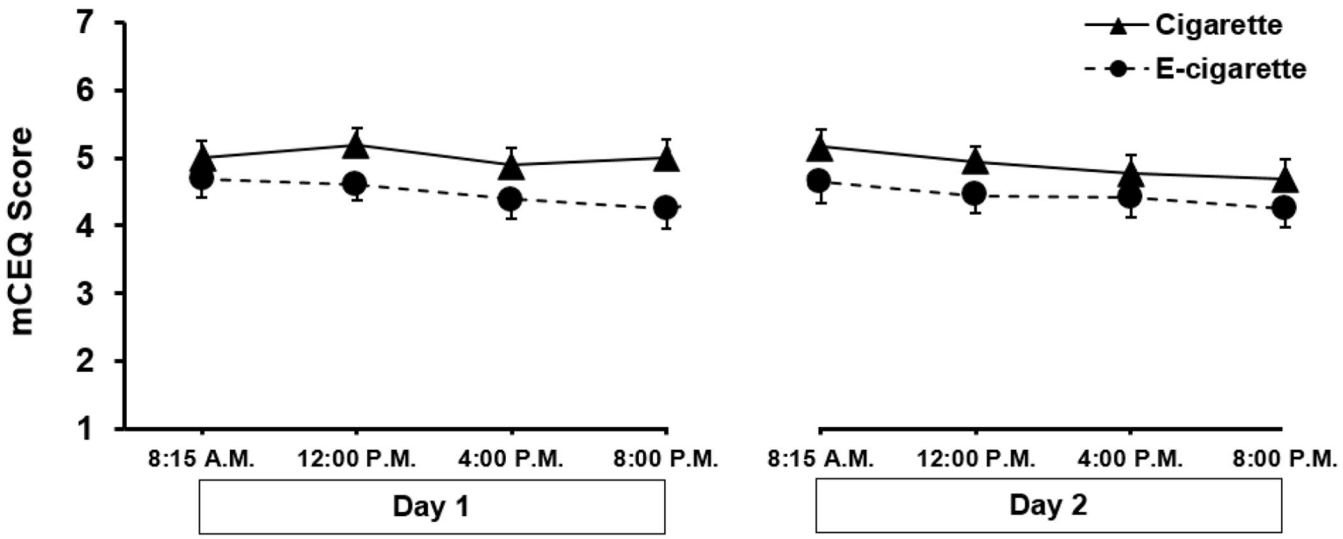

Figure 4. "Did smoking immediately relieve your craving for a cigarette?"

mCEQ Score = score for the item "did smoking immediately relieve your craving for a cigarette" on the modified cigarette evaluation questionnaire. Points represent raw values with standard error bars. Cigarettes were rated higher than e-cigarettes regardless of timepoint ($t[322]=6.87$, $p<.001$).

Table 1.

Demographic and E-cigarette and Cigarette Use Variables

	***N* = 36**
Demographic Variables	
Age, *mean (SD)*	35.4 (11.7)
Female, *N (%)*	8 (22.2)
Race, *N (%)*	
Asian	2 (5.6)
Black	3 (8.3)
Latino	4 (11.1)
Mixed	5 (13.9)
White	22 (61.1)
E-cigarette and cigarette Use Variables	
Device type, *N (%)*	
Cig-a-like	12 (33.3)
Fixed-power tank	15 (41.7)
Variable-power tank	6 (16.7)
Pod	3 (8.3)
Fagerstrom Test for Cigarette Dependence, *mean (SD)*	4.4 (2.0)
Penn State [Electronic] Cigarette Dependence Index, *mean (SD)*	5.9 (3.9)
Measured Liquid Nicotine Concentration, ug/mg, *mean, SD*	17.0 (12.9)
Cig-a-like	20.2 (13.4)
Fixed-power tank	12.2 (7.4)
Variable-power tank	9.4 (3.9)
Pod	43.4 (4.8)
Screening Salivary Cotinine, ng/ml, *geometric mean (CI)*	165 (142-193)
Cigarettes per day, *mean (SD)*	12.9 (6.4)
Number of days e-cigarettes used, *mean (SD)*	22.6 (7.3)
E-cigarette use, times per day, *mean (SD)*	8.1 (7.2)
Amount of e-cigarette liquid used per day (*N*=22), mL, *mean, SD*	3.6 (2.7)

‘Cigarettes per day,’ ‘number of days e-cigarettes used,’ and ‘e-cigarette times per day’ are based on self-reported use in the 30 days preceding the screening session. For ‘e-cigarette times per day’ participants were instructed to ‘assume that one “time” consists of around 15 puffs or lasts around 10 minutes.’ Amount of e-cigarette liquid used per day calculated for the 22 individuals reporting mL used per day.

Table 2.

Relationships with Nicotine Titration

	Statistic (*p*)
E-cigarette and cigarette use variables	
Penn State [Electronic] Cigarette Dependence Index, *r*	**0.50 (.002)**
Fagerstrom Test for Cigarette Dependence, *r*	−0.30 (.071)
Nicotine used per week, *milliliters* (*N* =22), *r*	0.12 (.600)
Liquid nicotine concentration, *r*	−0.10 (.551)
Device Type, *F*	0.84 † (.440)
Cigarettes per day, *r*	0.06 (.713)
Duration of e-cigarette use, *r*	0.07 (.693)
e-cigarette times per day, *r*	**0.49(.003)**
Average daily use of e-cigarettes compared to cigarettes, *r*	**0.56(<.001)**

Values represent Pearson correlation coefficients except † = ANOVA *F* statistic. Nicotine used per week was calculated by multiplying the percentage of nicotine typically used in e-cigarette liquids (22 individuals reported milliliters of liquid used per week) and milliliters of liquid typically used per day multiplied by 7. “e-cigarette times per day” is based on self-report of a ‘time’ meaning 15 puffs or ten minutes of e-cigarette use on days when an e-cigarette was used. “e-cigarette/cigarette” frequency calculated by: $\frac{\frac{(E-cigarette\ times\ per\ day)*(E-cigarette\ using\ days\ per\ month)}{30}}{Cigarettes\ per\ day}$.

Table 3.

Subjective Effects between Cigarettes and E-cigarettes

	Fixed Effects		Post-hoc Tests		
Dependent Variable	**Product Order *F* (*p*, f^2)**	**Product Type *F* (*p*, f^2, Bf^*)**	**Cigarette *m (SE)***	**E-cigarette *m (SE)***	***t* (*p*, *d*)**
Questionnaire of Smoking Urges					
E-cigarette - Desire and intention to smoke	0.81 (.369, <.001)	**25.58 (<.001, .074)**	16.82 (1.09)	18.97 (1.09)	**5.06 (<.001, .329)**
E-cigarette - Relief from negative affect by smoking	0.43 (.513, <.001)	**5.49 (.020, .012)**	10.75 (.73)	11.30 (.73)	**2.34 (<.001, .126)**
Cigarette - Desire and intention to smoke	**15.71 (<.001, .043)**	0.01 (.934, <.001, 0.09)	18.44 (1.05)	18.48 (1.05)	--
Cigarette - Relief from negative affect by smoking	2.07 (.151, .003)	1.01 (.316, <.001, 0.10)	11.07 (.72)	11.34 (.72)	--
Modified Cigarette Evaluation Questionnaire					
Smoking satisfaction	2.19 (.140, .001)	**11.49 (<.001, .031)**	14.74 (.50)	14.08 (.50)	**3.39 (<.001, .220)**
Psychological reward	**7.30 (.007, .022)**	**52.45 (<.001, .160)**	18.86 (.88)	16.58 (.88)	**7.24 (<.001, .432)**
Enjoyment of respiratory tract sensations	3.16 (.077, .002)	**11.37 (<.001, .017)**	4.19 (.24)	3.97 (.24)	**3.37 (<.001, .153)**
Craving reduction	0.02 (.894, <.001)	**47.17 (<.001, .093)**	5.03 (.20)	4.44 (.20)	**6.87 (<.001, .492)**
Aversion	0.94 (.333, <.001)	**9.55 (.002, .026)**	3.75 (.29)	3.41 3.75 (.29)	**3.09 (.002, .196)**
Positive and Negative Affect Scale					
Positive	**3.98 (.047, .011)**	3.63 (.058, .009, 0.12)	24.30 (1.72)	23.75 (1.72)	--
Negative	0.65 (.419, <.001)	0.08 (.780, <.001, 0.10)	13.11 (.29)	13.22 (.29)	--
Minnesota Nicotine Withdrawal Scale					
Total score	2.61 (.107, .006)	0.67 (.412, .001, 0.10)	7.92 (.88)	7.72 (.88)	--

Estimates for cigarette and e-cigarette are least squares means derived from the mixed model for each subjective effect score. *d* = Cohen's d. *Bf* = Bayes factor.

*Bayes factors estimated only when product type was not significant. Values in bold indicate they are associated with a significant effect (i.e. $p \leq .05$).

Table 4.

Subjective Effects between E-cigarette Types

	Fixed Effects			
Questionnaire	**E-cigarette Type *F* (*p*, f^2, *Bf**)**	**CAL *m (SE)***	**FP *m (SE)***	**VP *m (SE)***
Questionnaire of Smoking Urges				
E-cigarette - Desire and intention to smoke	1.13 (.324, <.001, 0.46)	15.23 (1.71)	18.76 (1.62)	18.34 (2.57)
E-cigarette - Relief from negative affect by smoking	1.71 (.181, <.001, 0.85)	9.09 (1.26)	12.18 (1.12)	11.31 (1.78)
Cigarette - Desire and intention to smoke	0.01 (.986, <.001, 0.19)	17.98 (1.80)	18.30 (1.61)	17.87 (2.54)
Cigarette - Relief from negative affect by smoking	0.90 (.406, <.001, 0.85)	9.87 (1.23)	12.08 (1.10)	10.99 (1.74)
Modified Cigarette Evaluation Questionnaire				
Smoking satisfaction	0.88 (.417, <.001, 0.47)	13.29 (.88)	14.71 (.79)	14.85 (1.25)
Psychological reward	1.01 (.365, <.001, 0.57)	15.67 (1.58)	18.52 (1.41)	16.13 (2.23)
Enjoyment of respiratory tract sensations	0.07 (.492, <.001, 0.53)	3.57 (.41)	4.05 (.36)	4.35 (.57)
Craving reduction	1.87 (.155, <.001, 0.87)	4.17 (.36)	5.10 (.32)	4.81 (.51)
Aversion	0.26 (.773, <.001, 0.35)	3.11 (.51)	3.58 (.45)	3.22 (.72)
Positive and Negative Affect Scale				
Positive	1.83 (.162, <.001, 1.60)	21.11 (2.92)	28.42 (2.61)	23.28 (4.13)
Negative	0.82 (.441, <.001, 0.72)	13.29 (.38)	13.26 (.45)	12.51 (.54)
Minnesota Nicotine Withdrawal Scale				
Total score	0.31 (.731, <.001, 0.37)	6.87 (1.59)	8.44 (1.42)	7.03 (2.24)

Estimates for e-cigarette types are least squares means derived from the mixed model for each subjective effect score. CAL= Cig-a-like, FP= Fixed-power tank, VP= Variable-power tank. f^2 = Cohen's f^2. *Bf* = Bayes Factor.