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Nicotine Replacement, Topography, and Smoking Phenotypes of E-cigarettes

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Abstract

Objectives—Little is known about the degree of nicotine replacement across first-generation e-cigarette brands, how e-cigarettes are used, and if there is variation across brands in relevant smoking phenotypes. The objective of this project was to collect data that are critical to better understanding, use, and exposure when using e-cigarettes, which may then inform clinical trials and tobacco regulatory policy.

Methods—Twenty-eight cigarette smokers were randomized to use one of 5 popular brands of e-cigarettes for a 10-day study. Day 1 (own cigarette brand) data established baseline levels for

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Human Subjects Statement
All participants provided signed informed consent. The protocol was approved by the University of Pennsylvania Institutional Review Board.

Conflict of Interest Statement
Dr Benowitz has served on scientific advisory boards for Pfizer and GlaxoSmithKline related to smoking cessation medications and has been an expert witness in litigation against tobacco companies. Dr Schnoll receives medication and placebo free of charge from Pfizer and has provided consultation to Pfizer and GlaxoSmithKline. These companies had no involvement in this study. Dr Strasser has received funding through the Pfizer GRAND program, an independent peer-reviewed grant program funded through Pfizer (2008-2011); all investigators have received funding from the United States National Institutes of Health.

cotinine, carbon monoxide (CO), topography, cigarette liking, withdrawal, and craving. Participants returned on Days 5 and 10 to reassess these measures while exclusively using e-cigarettes.

Results—Compared to cigarette smoking, e-cigarettes provided significantly lower nicotine levels (25%-50%), reduced CO exposure, and lower ratings of liking ($p < .05$). Topography significantly differed between cigarette and e-cigarette sessions ($p < .05$). All brands significantly reduced withdrawal and craving ($p < .05$). There were no significant brand differences in outcome measures associated with exposure or use.

Conclusions—E-cigarettes are not liked as much as cigarettes, provide significantly lower nicotine replacement, reduce CO exposure, and mitigate withdrawal and craving. The patterns of use significantly differ compared to cigarette smoking.

Keywords

e-cigarette; cotinine; smoking behavior; vaping; nicotine craving; nicotine withdrawal

Despite widespread awareness of the harms of tobacco use, approximately 17% of the United States (US) population continues to smoke cigarettes.[1] Upwards of 70% of current smokers would like to quit smoking[2] and 30% to 40% of smokers make a serious quit attempt each year.[3] However, approximately 80% of smokers who make an unassisted quit attempt relapse within the first month and only about one-third of smokers who use medications approved by the US Food and Drug Administration (FDA) to quit smoking are successful.[4] Thus, novel treatments for nicotine dependence treatment are needed to address the relatively stable national prevalence of cigarette smoking seen over the last decade.[2] Research reports that e-cigarettes are being used by cigarette smokers for a myriad of reasons, including reducing their amount of cigarette smoking, ceasing cigarette use altogether, or taking in nicotine in locations where cigarette use is prohibited. First-generation cigalike devices often serve as an entry point into vaping, thereby increasing the need to understand their use patterns relative to smoking.[5] This flexibility of reasons to use, and the occurrence of poly-use of nicotine-containing products begin to blur the dichotomy of smoker versus non-smoker to an evolving, more nuanced continuum of nicotine-containing product use.[6-8]

Electronic cigarettes (e-cigarettes) have been gaining in popularity as a potential option for reducing tobacco use or quitting smoking since they were introduced in the US in 2007. E-cigarette sales are now about 0.5% of the tobacco market (accounting for $500 million/year) and projections indicate a doubling of the market share in the coming years.[9] The e-cigarette, which is a battery-powered device that delivers an aerosol containing nicotine without combustion, is marketed and perceived by many as a “safer” alternative to cigarettes and as a potential method for quitting smoking. Furthermore, health concerns regarding e-cigarettes’ enabling youth initiation of nicotine use, renormalization of smoking, dual use of tobacco products, and the need to evaluate whether e-cigarettes are a less harmful nicotine product for smokers have been raised.[10,11] Many of these claims and concerns are widespread despite a paucity of carefully-controlled studies examining safety and efficacy.[12]

In 2013, the US National Institutes of Health sponsored an e-cigarette workshop to inform and promote research on e-cigarettes. A summary of this endeavor calls for increased empirical knowledge that can inform regulatory efforts regarding this emerging public health issue.[13] Three of the several key research areas identified were to: (1) characterize how e-cigarettes are used and the best methods to assess use; (2) characterize the delivery of nicotine; and (3) to improve evaluation of the potential role for e-cigarettes in smoking cessation trials. These priorities have become heightened given the FDA's move to bring e-cigarettes under their regulatory authority.

There are at least 2 issues that could have important implications for the use of e-cigarettes. First, there are few data on the degree to which e-cigarettes provide adequate replacement of nicotine, particularly first-generation devices, compared to regular cigarettes.[14] Adequate nicotine replacement is beneficial for alleviating withdrawal symptoms that trigger relapse to smoking if the product is to be used for long-term cessation.[15] Second, there are limited data on the degree to which e-cigarettes provide consistent nicotine replacement over the course of time.[16] Examining the degree to which e-cigarettes replace nicotine levels compared to smoking cigarettes, and characterizing nicotine levels over a period of time would be important in the drug evaluation process. As Hitchman et al[10] note, first-generation devices may deliver less nicotine than second-generation tank devices, which may make them less effective at smoking cessation. At the same time, their similar physical appearance may make them highly appealing to cigarette smokers in reducing craving.[17] Seidenberg et al[18] reported that first-generation cigalike brands owned by cigarette companies appear to be implicitly marketed as a dual use or switching product, making the need to characterize use patterns when switching more relevant.

Thus, this study was designed to assess 3 critical issues: (1) to determine the degree to which use of 5 popular brands of first-generation e-cigarettes over the course of 9 days yields nicotine levels compared to cigarette smoking; (2) to determine whether these nicotine levels are consistent over time; and (3) to characterize how e-cigarettes are puffed (or vaped) compared to cigarette smoking in a US-based sample of current smokers who switch to e-cigarettes using video scoring methods. Several variations in customized mouthpiece devices have been utilized to assess vaping behavior and to characterize use patterns.[18,19] However, the need to use modified mouthpieces may mean that different mouthpieces must be used for each product used (cigarette, first-generation cigalikes, tanks) which could affect use patterns, perhaps not systematically, thereby complicating comparisons across tobacco products. Furthermore, the growing prevalence of dual users of cigarettes and e-cigarettes means that future studies examining patterns of use ostensibly need an objective measure across multiple products with identical procedures to minimize potential confounds. There are solid data demonstrating the popularity of first-generation (cigalike) devices.[10] Equally important, upwards of 63% of first-generation e-cigarette users progress to advanced-generation devices,[5] and having a common method to compare use patterns as a result of device changes has potential value in understanding who switches and how their behavior changes as a result of switching. In summary, establishing a method that can be used to characterize use patterns in first- and advanced-generation electronic devices, as well as combustible cigarettes, allows for the examination of poly-use patterns and product switching patterns that may be important for understanding individual level changes.

Applying rigorous scoring to digital video files of smoking and vaping behavior may serve as a low cost, reliable alternative that allows comparisons among product types.

Secondarily, assessment of withdrawal and craving, the direct rewarding effects of nicotine (eg, stimulation) and the cigarette (eg, satisfying), carbon monoxide levels, and topographic and daily use patterns were assessed and compared over time and among brands. These data can help to determine the most appropriate e-cigarette brand to select for subsequent testing of safety and efficacy using a placebo-controlled randomized trial and to inform regulatory gaps identified by the research community related to understanding e-cigarette use patterns, now that e-cigarettes will be regulated in the US by the FDA.

METHODS

Procedures

This was a randomized, factorial design, with a between subjects factor (5 different brands of e-cigarettes) and a within-subject factor (tobacco product used: one session of usual brand cigarettes on Day 1, and 2 sessions of e-cigarette use on Days 5 and 10). The study used a similar study design as used by Eissenberg et al[15] for assessing e-cigarettes, and by Goniewicz et al[21] and others to examine smoking behavior differences across tobacco products.[22,23] The study was conducted in 3 sessions: Day 1 (usual brand cigarette smoking) and Days 5 and 10 (single brand of e-cigarette use). Following Day 1, participants were required to refrain from using regular cigarettes and were asked to use the provided brand of e-cigarette; an assessment of breath carbon monoxide (CO) was conducted to verify refraining from cigarette use (≤10 ppm on Day 5 and Day 10), using a cut-off for cigarette smoking abstinence often used in clinical trials.[24,25] Participants were randomized to one of the 5 brands of e-cigarettes. The brands were selected based on an assessment of evaluations and rankings posted on e-cigarette websites and forums, as done previously,[21] that also represented commercially popular and strongly rater supported versions to obtain a reasonable cross-sectional sample of the market.[8] These brands have been selected for previous research on first-generation design e-cigarette brands (cigalike).[15,26,27] The 5 brands selected, including brand reported nicotine levels, were: (1) *NJOY* (www.njoy.com), 18mg nicotine; (2) *V2* (www.v2cigs.com), 18mg nicotine; (3) *Green Smoke* (www.greensmoke.com), 18.9-20.7mg nicotine; (4) *blu* (www.blucigs.com), 20-24mg nicotine; and (5) *White Cloud* (www.whitecloudelectroniccigarettes.com), 23-24 mg nicotine. Each brand advertised the delivery of the same level of nicotine (appropriate for about a pack/day smoker), provided the standard tobacco flavor, and used a disposable cigarette-like device.

Media ads were used to enroll current daily cigarette smokers. Participants were age 18 to 65 and self-reported smoking at least 10 cigarettes per day. Exclusion criteria included: use of other tobacco or nicotine-containing products, including e-cigarettes (no more than 3 previous episodes of use and not currently using), current diagnosis or evidence of substance abuse or dependence or major depression, current or history of psychotic or bipolar disorder, history of suicide attempt, history of cancer or cardiovascular disease, uncontrolled hypertension, use of smoking cessation medications or any current plans to try to quit

smoking, or current pregnancy or lactation. Participants were informed through telephone screening that standard tobacco flavor would be the only flavor available.

Once determined eligible, participants were scheduled for the first testing session (Day 1). For all sessions, participants were requested to abstain from smoking for 2 hours prior to the session. To begin, a saliva sample was collected to determine baseline cotinine levels. Measures of withdrawal and craving were assessed and breath CO was ascertained. Then participants were allowed to smoke their own regular brand of cigarette. Next, 4 minutes post-smoking, a second breath CO was taken and withdrawal and craving measures were reassessed. In addition, participants completed 2 measures to assess: (1) the direct effects of nicotine (eg, dizzy, nauseas, headache); and (2) the direct effects of the cigarette (eg. satisfying, calming, pleasant, smoke another right now), as done previously.[15] Smoking sessions were digitally recorded and topography use measures later extracted using trained raters and a procedure previously used to characterize cigarette smoking.[28] Participants were provided with their supply of e-cigarettes based on randomization and instructed to refrain from any tobacco/nicotine use aside from the e-cigarette provided for the remaining 9 study days. Participants were instructed to use a daily diary to track the frequency of e-cigarette use episodes each day from Day 2 to Day 10, and to use their assigned e-cigarette as much as desired.

Participants were asked to return to the study site on Days 5 and 10 for 2 identical testing sessions; all sessions were scheduled for the same time of day. These sessions followed the exact procedures as described above for Day 1, except that the brand of randomized e-cigarette was used and participants were instructed to use the e-cigarette *ad libitum* during a 10-minute vaping period in place of the cigarette smoking period on Day 1. Participants were ineligible to continue in the study if they self-reported smoking regular cigarettes on study Days 2-10 or provided a CO greater than 10ppm on Days 5 or 10. Successful completion of all study sessions and study-related tasks resulted in $180 remuneration.

Measures

Demographic and smoking-related characteristics—Participants completed self-report measures of demographics (eg, race, sex) and smoking history and behavior (eg, cigarettes per day and Fagerström Test for Nicotine Dependence [FTND]).[29]

Cotinine levels—A 5ml saliva sample was collected at each testing session to assess cotinine levels as a measure of nicotine. Samples were assessed by the University of California, San Francisco using gas chromatography.[30]

Withdrawal symptoms and cravings—The Withdrawal Symptom Checklist[31] measured withdrawal symptoms associated with quitting smoking. The Likert-style scale assesses 10 DSM-IV items of nicotine withdrawal (eg, restlessness, irritability). Craving was assessed by the well-validated 10-item Questionnaire of Smoking Urges (QSU-B).[32] Items for each scale were summed for total scores on withdrawal and craving.

The direct effects of nicotine and e-cigarettes—Participants completed 2 measures to assess: (1) the direct effects of nicotine (eg, dizzy, nausea, headache); and (2) the direct

effects of the e-cigarette (eg, satisfying, calming, pleasant, smoke another right now), as done previously.[15] These questionnaires use visual analog scales with a single word scored from 0 (not at all) to 100 (extremely). Total scores were summed for each scale such that higher scores for the nicotine measure indicated negative responses and higher scores for the e-cigarette measure indicated positive responses.

E-cigarette use/topography—Multiple measures of product use were collected: (1) total number of puffs (cigarette Day 1) and total number of e-cigarette vapes (Days 5 and 10) were assessed; (2) puff and vape duration, defined as the length of time of each puff or vape and measured in seconds; (3) interpuff (intervape) interval, defined as the length of time between puffs or vapes and measured in seconds; and (4) total time of use, defined as the time from first use (puff or vape) of the product until the end of the last puff or vape, measured in seconds, was extracted from digital video recordings from each 10-minute *ad libitum* use laboratory session by a group of 3 trained raters. The 10-minute duration of cigarette smoking (Day 1) and vaping periods in the lab was based on previous laboratory-based research of smoking behaviors and e-cigarette vaping studies.[20,28,33]

Smoking and vaping digital-recorded sessions were reviewed by a team of 3 trained raters using video editing software (VideoSpirit Pro, Softpedia.com) to mark puffing and vaping events. The digital timer feature was used to determine duration of events (puffs, interpuff interval) and frequency count for number of puffs was recorded manually. A puff was operationalized as the e-cigarette being placed in the mouth and the onset and offset of the mouth drawing on the cigarette (Day 1) and e-cigarette (Days 5 and 10) as the beginning and ending to determine duration. The time between puffs was the interpuff interval.[28]

Participants also were asked to track the number of vaping episodes each day from Day 2 to Day 10 using a study calendar provided to them, modified for e-cigarette use and based on daily cigarette use tracking following time line follow back procedures.[22]

Data Analysis

The participants were characterized in terms of demographic and smoking-related data (eg, age, race, level of nicotine dependence, and smoking rate). Intraclass correlation coefficients were calculated to determine reliability of cigarette and e-cigarette topography data extracted from the digital video files by the raters. We compared the cotinine levels at the measurement time-point across sessions (Days 1, 5, and 10) and across e-cigarette brands. Percent nicotine replacement was assessed from the ratio of saliva cotinine at week 5 or 10 over baseline. A mixed factorial ANOVA was used to assess condition (within: regular cigarette vs brands of e-cigarette) by time (between: Days 1, 5, 10) interaction effects (and main effects) on cotinine levels. *Post hoc* Tukey tests were used to determine significance of differences in cotinine levels between the e-cigarette brands and regular cigarettes and across the time-points. Next, a one-sample t-test analysis was conducted to assess stability of cotinine during e-cigarette use by using the difference of Day 10 and Day 5 cotinine levels, compared to a hypothesized difference of 0. Lastly, a mixed factorial ANOVA was used to assess condition (regular cigarette vs brands of e-cigarette) by time (Days 1, 5, 10) interaction effects (and main effects) on CO levels, topography measures, overall withdrawal

and craving (pre-session levels), nicotine and e-cigarette effects, and change in withdrawal and craving (pre-session vs post-session).

RESULTS

Sample Characteristics

Twenty-eight participants were enrolled and randomized to one of 5 brands of e-cigarettes (Table 1). The first 4 participants randomized to *NJOY* experienced malfunctioning e-cigarettes, and withdrew from the study (the product was removed from the market before the fifth participant was randomized). Although their demographic data appear in Table 1, the remaining analyses were performed using data from only the other 4 e-cigarette brands. Most of the sample were males (75%), Caucasian (79%), and not married (68%). The sample was about evenly split in terms of possessing a college degree (54%) versus not (46%), and making more (54%) or less (46%) than $35,000/year. Mean (SD) baseline saliva cotinine was 265ng/ml (122), the average number of cigarettes per day at baseline was 16.9 (6.6), the average age at which participants started to smoke was 12.6 (4.7), the average FTND score was 3.8 (1.6), and the baseline CO was 16.7ppm (8.7). There were no differences in these variables across the e-cigarette brands. For *blu*, *Green Smoke*, and *V2*, 83% of participants completed the 10-day study; only 33% of participants randomized to *White Cloud* completed the 10-day study. No participants were excluded from the study due to non-compliance, specifically CO > 10ppm or self-reported continued cigarette smoking at Day 5 or 10. Non-completion was attributable to participants electing to withdraw and not attend a laboratory session. Of the 7 who did not complete all sessions, 4 had been randomized to *White Cloud* and one each to *blu*, *Green Smoke*, and *V2*.

Nicotine Replacement over Time and between E-cigarette Brands

There was no main effect for e-cigarette brand or an interaction effect for brand by time ($p > .05$). There was a main effect for time, indicating that for all e-cigarette brands, the level of cotinine was significantly reduced from Day 1 (regular cigarettes) to Day 10 ($F[2,12] = 13.4$, $p = .001$). Relative to baseline cotinine from the participants own brand of cigarettes, percent change at Day 5 (on e-cigarettes) ranged from 34.2% (*blu*) to 54.7% (*Green Smoke*), and change at Day 10 (on e-cigarettes) ranged from 23.4% (*White Cloud*) to 56.3% (*V2*) (Table 2). There were no main or interaction effects for cotinine levels within the e-cigarette period (Day 5 vs Day 10, $ps > .05$). Relative to Day 5, the percent change at Day 10 ranged from 124% (*V2*) to 43% (*White Cloud*) (Table 2). In support of the consistency of cotinine levels during the e-cigarette period, the within-subject change in cotinine values between Days 5 and 10 were not statistically different [$t(16)=.024$, $p = .98$].

Withdrawal, Craving, Nicotine and E-cigarette Effects

There were no main or interaction effects for withdrawal assessed prior to each session ($p > .05$). For pre-session craving, there was no main effect for e-cigarette brand or an interaction effect, but there was a main effect for time. Craving, assessed prior to the Day 1 session, was significantly greater ($M = 35.1$; $SE = 3.5$) than craving assessed prior to the Day 5 ($M = 32.4$; $SE = 3.4$) and Day 10 ($M = 28.4$; $SE = 3.7$) ($F[2,12] = 4.3$, $p = .04$) sessions.

In terms of the direct effects of nicotine from e-cigarette use during each session, there were no main or interaction effects ($p > .05$), indicating that participants reported similar effects from the e-cigarette brands, and relative to smoking their own cigarette on Day 1. There was, however, a main effect for time on the measure "assessing e-cigarette liking" ($F[2,12] = 23.8$, $p < .001$). Relative to self-reported liking assessed at Day 1 ($M = 627.0$; $SE = 43.0$; in reference to their own cigarette), reports of liking of the e-cigarette were significantly lower at Day 5 ($M = 340.4$; $SE = 31.2$) and Day 10 ($M = 343.6$; $SE = 39.6$). There was no main effect for e-cigarette brand or an interaction effect for e-cigarette liking ($p > .05$).

E-cigarette Topography and Use

There were no significant differences in the number of daily e-cigarette episodes relative to cigarette smoking ($p > .05$). Average daily use of the e-cigarettes by brand between Day 2 (first full day of e-cigarette use) and Day 10 [*blu* ($M = 15.7$, $SD = 6.7$), *Green Smoke* ($M = 19.1$, $SD = 7.8$), *V2* ($M = 15.4$, $SD = 6.4$), and *White Cloud* ($M = 11.3$, $SD = 4.5$)] was not statistically different ($p > .05$).

The average number of puffs (or vapes) were 13.6 ($SD = 4.0$), 16.1 ($SD = 11.9$), and 13.2 ($SD = 9.4$) for the Days 1, 5, and 10 *ad libitum* sessions, respectively ($p = .86$). One participant took 49 vapes on Day 5, resulting in a relatively larger mean and standard deviation; exclusion of these data did not affect significance levels and therefore, were included. Average puff (vape) duration times were 1.64 seconds ($SD = 0.3$), 1.99 seconds ($SE = 0.7$), and 2.06 seconds ($SE = 0.7$), for Days 1, 5, and 10, respectively ($F[1,16] = 6.03$, $p = .026$). Average interpuff (intervape) intervals were 25.3 seconds ($SD = 13.3$), 11.2 seconds ($SD = 5.2$), and 11.2 seconds ($SD = 5.2$) for Days 1, 5, and 10, respectively ($F[1,16] = 16.68$, $p = .001$). Average time of use, from the first puff or vape to the last, was 321.4 seconds ($SD = 108$), 178.6s ($SD = 113.2$), and 165.6 seconds ($SD = 89.5$), for Days 1, 5, and 10, respectively ($F[1,16] = 40.90$, $p = .001$). There were no significant differences in topography by e-cigarette brand. Intraclass correlation coefficient analyses of the 3 trained raters for the topography measures was excellent (ICC = .84, 95% CI = .78-.91, $p = .005$).

Lastly, for CO levels, although there was no main effect for e-cigarette brand or interaction effect, there was a significant main effect for time ($F[1,16] = 12.8$, $p = .001$). On Day 1 (smoking usual brand), average pre-session CO level was 15.6ppm ($SE = 2.5$), compared to 2.7ppm ($SE = 0.5$) on Day 5 and 3.3ppm ($SE = 0.9$) on Day 10 when e-cigarettes were used. CO boost (the difference in CO post and pre-session was significantly different: 3.6ppm ($SE = 3.12$) for Day 1 compared to 0.00ppm ($SE = .47$) and 0.06ppm ($SE = 0.96$) at Days 5 and 10, respectively ($F[1,16] = 17.44$, $p = .001$).

Change in Withdrawal and Craving with Sessions

E-cigarette use on Day 5 significantly reduced levels of withdrawal ($F[1,13] = 9.9$, $p = .008$), as examined by the change in withdrawal after e-cigarette use. Whereas there was no variation in the degree to which e-cigarette use alleviated withdrawal at the Day 5 session across the brands ($p > .05$), withdrawal levels dropped from an average of 8.4 ($SE = 1.5$) at the start of the session to 5.7 ($SE = 1.5$) following e-cigarette use. The results were similar for the Day 10 session, with withdrawal levels dropping from an average of 7.9 ($SE = 1.3$) at

the start of the session to 4.3 (SE = 1.0) following e-cigarette use ($F[1,13] = 13.5$, $p = .003$). Furthermore, e-cigarette use on Day 5 significantly reduced levels of craving ($F[1,14] = 10.7$, $p = .006$). Although there was no variation in the degree to which e-cigarette use alleviated craving at the Day 5 session across the brands ($p > .05$), craving levels dropped from an average of 32.8 (SE = 3.1) at the start of the session to 21.6 (SE = 2.6) following e-cigarette use. The results were similar for the Day 10 session, with craving levels dropping from an average of 28.4 (SE = 3.7) at the start of the session to 20.9 (SE = 3.2) following e-cigarette use ($F[1,13] = 20.3$, $p = .001$).

DISCUSSION

This study reports on the changes in use patterns, cotinine levels, and psychological and subjective responses when daily cigarette smokers with limited e-cigarette experience switch to a first-generation e-cigarette. Many users enter the e-cigarette market using first-generation devices, and as such, it was important to examine these changes closely. Vaping behavior differed significantly from smoking behavior and the video scoring procedure used in all laboratory sessions appears to be a reliable non-invasive means to characterize vaping objectively. Cotinine levels significantly decreased during vaping compared to cigarette smoking and did not differ by brand type. By measuring cotinine during cigarette smoking we allow each participant to serve as his or her own control to compare relative cotinine levels during vaping. It is worth noting that given a 9-day period to use the product *ad libitum*, cotinine levels did not approach levels observed during the cigarette-smoking period.

The purpose of this study was 3-fold. First, we sought to determine the degree to which use of 5 popular brands of e-cigarettes over the course of 9 days allows cigarette smokers to maintain nicotine levels, compared to cigarette smoking. Results from this study indicate that over a 9-day duration of e-cigarette use, smokers' saliva cotinine levels were between 23% and 55% of cotinine levels observed when smoking their usual brand cigarettes, representing a significant decrease in nicotine consumption. These results must be weighed against the apparent differences in study completion by brand as those randomized to *blu*, *Green Smoke*, and *V2* had little attrition, a stark contrast to the high attrition in those randomized to *White Cloud* and the product failure of *NJOY*. Product use compliance was high and CO levels significantly lower during e-cigarette use, suggesting that for those who were able to complete the study there was negligible cigarette smoking. Withdrawal and craving were significantly decreased after using the e-cigarettes further supporting their potential utility as a smoking cessation aid. As such, these indicators of similarity across brands in how nicotine is replaced relative to baseline smoking suggest that clinical trials testing efficacy of e-cigarettes would not be significantly confounded by which brand of first-generation cigalike e-cigarette is selected.

The second purpose of this study was to determine whether cotinine levels are consistent over time. For those completing all sessions, cotinine levels were not significantly different between Days 5 and 10, thereby supporting the stability of cotinine levels during early use of e-cigarettes during a 10-day period. This is an important issue for users and researchers interested in evaluating the efficacy and acceptability of e-cigarettes. Whereas the levels of

nicotine replacement relative to smoking are considerably lower, there appears to be consistency in cotinine levels achieved over time, supporting the reliability of dosing over time. This consistency also may suggest that modifications in use (eg, instructing the user to take longer vapes or more frequent vapes) or modifications in product design could yield better overall nicotine replacement across users.[10] Further research should examine how individual differences affect variability in users' cotinine levels as well as use patterns of electronic cigarettes.

The third purpose of the study was to characterize how e-cigarettes are used compared to cigarette smoking in a US-based sample of current smokers who switch to e-cigarettes. As noted in a review of e-cigarette research by Evans and Hoffman,[34] only 5 peer-reviewed papers had at that time examined e-cigarette topography, and of those, only one by Farsalinos et al[35] employed in-person, objective measurement of smoking behaviors, albeit in a single-exposure design. More recent work in vaping topography has utilized modified mouthpieces added to existing cigarette topography devices,[36] or custom devices that users report impact their e-cigarette use.[19] Results from this study report e-cigarette topography over 2 sessions of use and in comparison to their cigarette smoking behavior. Video recorded methods have advantages over modified mouthpieces that have not been validated for use on electronic cigarettes, or custom devices that may affect actual use patterns, thereby compromising external validity.[19] Scored video recordings are non-invasive, relatively low cost, can be used to compare across tobacco product types (cigarettes, cigalikes, tank products) and as reported herein, are highly reliable.

Our results suggest that e-cigarette use is significantly different than cigarette smoking behavior. Participants took similar numbers of puffs or vapes across all sessions, but each puff was of longer duration (approximately 20% longer puff duration), and at shorter intervals between puffs (25.3 seconds vs 11.2 seconds). Longer duration and more frequent puffs may have implications for constituent exposure. Previous research has noted the need for a relatively higher negative pressure when puffing e-cigarettes compared to conventional cigarettes.[27] Higher negative pressure can be achieved by employing more intense vaping topography. Although this study was not powered or designed to examine the relationship between behavior and exposure, we do observe significant negative correlations between intervape interval at Days 5 and 10 with cotinine levels at study completion ($r = -.52$, $p = .03$). Furthermore, duration of e-cigarette use within the *ad libitum* sessions was approximately half of the time participants smoked cigarettes. This finding is not surprising and illustrates one of the prime marketing themes of e-cigarettes: flexibility to use however and whenever the user desires.

There are a few limitations to note. First, the study had a small sample size and was not recruited to represent all types of e-cigarette users. All participants were current daily cigarette smokers with no or minimal prior e-cigarette use experience and who were willing to switch to e-cigarettes for 10 days; thus, the sample represents only one group of e-cigarette adopter. A second limitation is the product failure and subsequent discontinuation of production of the *NJOY* product used in this study. Third, although biochemically-supported by am bient level CO levels and positive cotinine levels, exclusive e-cigarette use was based on self-report. Fourth, the project was restricted to using only 5 popular cigarette-

like brands of e-cigarettes and results should not be extended to newer-generation devices, or other variations of the brands studied that also used flavorings. Second- and third-generation devices that deliver higher doses of nicotine are growing in popularity, and some users will switch between device types after beginning e-cigarette use by using first-generation devices.[5] However, this limitation must be tempered by the fact that there are over 460 brands of e-cigarettes and approximately 10 new brands being introduced each month,[37] making examination of all brands in one study infeasible. Our selections were based on commercial and user popularity of specific brands, and did not investigate the array of flavors available in these products.

Although cigarette-like e-cigarettes were not liked as much as regular cigarettes and provided significantly lower nicotine replacement than regular smoking, they also provided consistent nicotine replacement over time, significantly reduced CO exposure, and mitigated withdrawal and craving. Importantly, there were no differences in nicotine replacement or any smoking phenotype assessed across the e-cigarette brands evaluated. Topography measures were characterized using an objective, non-obstructive method (video recording) and results demonstrate the differences in e-cigarette use compared to cigarette smoking when both are given *ad libitum* use of the product. Empirical knowledge in these areas, as reported herein, is critically needed to inform the discourse on possible regulatory efforts regarding e-cigarettes.[13,34]

IMPLICATONS FOR TOBACCO REGULATION

Understanding use patterns of tobacco products is an important component of assessing the impact the product has on public health. Electronic cigarettes pose a unique challenge because there is significant variation in product design features that make them different than cigarettes. Objective measurement of smoking and vaping, such as topography devices, use modified mouthpieces or custom devices that have not gone through rigorous testing and users report difficulty in using. This paper reports on a study that used scoring of digital video files of smoking and vaping to characterize use. Our study also reports on subjective and biochemical measures associated with use when cigarette smokers are switched to first-generation cigalike devices. Results from this study contribute to tobacco regulatory research by providing a noninvasive, low cost means to measure use behavior. It also provides biobehavioral outcome measures to compare cigarette smoking to vaping electronic cigarettes when cigarette smokers switch products. Given the FDA's new authority to regulate e-cigarettes, it will be increasingly important to characterize how e-cigarettes are used. Moreover, given the popularity of e-cigarettes as a potential means to reduce cigarette smoking for some users, while concurrently being a popular product for youth and less inveterate smokers, understanding use patterns, exposure, and subjective responses is needed for more thorough examination of how tobacco regulations affect all populations of user.

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References

1. US Centers for Disease Control and Prevention (CDC). Tobacco product use among adults – United States, 2012-2013. MMWR Morb Mortal Wkly Rep. 2014; 63(25):542–547. [PubMed: 24964880]
2. US Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults – United States, 2005-2012. MMWR Morb Mortal Wkly Rep. 2014; 63(2):29–34. [PubMed: 24430098]
3. Fiore MC, Jaen CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update US Public Health Service clinical practice guideline executive summary. Respir Care. 2008; 53:1217–1222. [PubMed: 18807274]
4. Stead L, Lancaster T. Combined pharmacotherapy and behavioural intentions for smoking cessation. Cochrane Database Syst Rev. 2012; 10:CD008286. [PubMed: 23076944]
5. Yingst JM, Veldheer S, Hrabovsky S, et al. Factors associated with electronic cigarette users' device preferences and transition from first generation to advanced generation devices. Nicotine Tob Res. 2015; 17:1242–1246. [PubMed: 25744966]
6. King BA, Alam S, Promoff G, et al. Awareness and ever use of electronic cigarettes among US adults, 2010-2011. Nicotine Tob Res. 2013; 15:1623–1627. [PubMed: 23449421]
7. Giovenco DP, Lewis MJ, Delnevo CD. Factors associated with e-cigarette use: a national population survey of current and former smokers. Am J Prev Med. 2014; 47(4):476–480. [PubMed: 24880986]
8. Giovenco DP, Hammond D, Corey CG, et al. E-cigarette market trends in traditional US retail channels, 2012-2013. Nicotine Tob Res. 2015; 17:1279–1283. [PubMed: 25542918]
9. Alderman, L. [July 23, 2016] E-cigarettes are in vogue and at a crossroads. Available at: http://www.nytimes.com/2013/06/13/business/e-cigarettes-are-in-vogue-andat-a-crossroads.html?pagewanted=all&_r=0.
10. Hitchman SC, Brose LS, Brown J, et al. 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]
11. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. JAMA. 2015; 314(7):700–707. [PubMed: 26284721]
12. Trtchounian A, Talbot P. Electronic nicotine delivery systems: is there a need for regulation? Tob Control. 2011; 20:47–52. [PubMed: 21139013]
13. Walton KM, Abrams DB, Bailey WC, et al. NIH electronic cigarette workshop: developing a research agenda. Nicotine Tob Res. 2015; 17(2):259–269. [PubMed: 25335949]
14. Etter JF, Bullen C, Flouris AD, et al. Electronic nicotine delivery systems: a research agenda. Tob Control. 2011; 20:243–248. [PubMed: 21415064]
15. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev. 2010; 19:1945–1953. [PubMed: 20647410]
16. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the "e-cigarette.". Am J Public Health. 2010; 100:2340–2342. [PubMed: 21068414]
17. Dawkins L, Munafo M, Christoforou G, et al. The effects of e-cigarette visual appearance on craving and withdrawal symptoms in abstinent smokers. Psychol Addict Behav. 2016; 30(1):101–105. [PubMed: 26415054]
18. Seidenberg AB, Jo CL, Ribisl KM. Differences in the design and sale of e-cigarettes by cigarette manufacturers and non-cigarette manufacturers in the USA. Tob Control. 2015; 25:e3–e5. [PubMed: 26546151]
19. Spindle TR, Breland AB, Karaoghlanian NV, et al. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. Nicotine Tob Res. 2015; 17(2):142–149. [PubMed: 25239957]
20. Farsalinos KE, Spyrou A, Tsimopoulou K, et al. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. Sci Rep. 2014; 4:4133. [PubMed: 24569565]

21. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014; 23(2):133–139. [PubMed: 23467656]
22. Strasser AA, Ashare RL, Kaufman M, et al. The effect of menthol on cigarette smoking behaviors, biomarkers and subjective responses. Cancer Epidemiol Biomarkers Prev. 2013; 22:382–389. [PubMed: 23334588]
23. Mercincavage M, Souprountchouk V, Tang KZ, et al. A randomized controlled trial of progressively reduced nicotine content cigarettes on smoking behaviors, biomarkers of exposure, and subjective ratings. Cancer Epidemiol Bio-markers Prev. 2016; 25(7):1125–1133.
24. Society for Research on Nicotine and Tobacco, Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002; 4:149–159. [PubMed: 12028847]
25. Schnoll RA, Hitsman B, Blazekovic S, et al. Longitudinal changes in smoking abstinence symptoms and alternative reinforcers predict long-term smoking cessation out comes. Drug Alcohol Depend. 2016; 165:245–252. [PubMed: 27372219]
26. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. Tob Control. 2010; 19(1):87–88. [PubMed: 20154061]
27. Trtchounian A, Williams M, Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. Nicotine Tob Res. 2010; 12:905–912. [PubMed: 20644205]
28. Strasser AA, Tang KZ, Sanborn PM, et al. Behavioral filter vent blocking on the first cigarette of the day predicts which smokers of light cigarettes will increase smoke exposure from blocked vents. Exp Clin Psychopharmacol. 2009; 17:405–412. [PubMed: 19968405]
29. 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; 86:1119–1127. [PubMed: 1932883]
30. Jacob P, Yu L, Wilson M, Benowitz NL. Selected ion monitoring method for determination of nicotine, coti-nine and deuterium-labeled analogs: absence of an isotope effect in the clearance of (S)-nicotine-3',3'-d2 in humans. Biol Mass Spectrom. 1991; 20:247–252. [PubMed: 1883864]
31. Hughes JR, Hatsukami DK, Pickens RW, Svikis DS. Consistency of the tobacco withdrawal syndrome. Addict Behav. 1984; 9:409–412. [PubMed: 6532150]
32. Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. Br J Addict. 1991; 86:1467–1476. [PubMed: 1777741]
33. Breland AB, Kleycamp BA, Eissenberg T. Clinical laboratory evaluation of potential reduced exposure products for smokers. Nicotine Tob Res. 2006; 8:727–738. [PubMed: 17132520]
34. Evans SE, Hoffman AC. Electronic cigarettes: abuse liability, topography and subjective effects. Tob Control. 2014; 23(Suppl 2):ii23–ii29. [PubMed: 24732159]
35. Farsalinos KE, Romagna G, Tsiapras D, et al. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. Int J Environ Res Public Health. 2013; 10:2500–2514. [PubMed: 23778060]
36. Lee YH, Gawron M, Goniewicz ML. Changes in puffing behavior among smokers who switched from tobacco to electronic cigarettes. Addict Behav. 2015; 48:1–4. [PubMed: 25930009]
37. Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control. 2014; 23(S3):iii3–iii9. [PubMed: 24935895]

Table 1

Baseline Characteristics of Sample

	blu (N = 6)	Green Smoke (N = 6)	NJOY (N = 4)	V2 (N = 6)	White Cloud (N = 6)	p
Gender (% Female)	33.3	33.3	0	16.7	33.3	.53
Race (% Caucasian)	83.3	83.3	75.0	83.3	66.7	.94
Age (m/SD)	46.8 (12.5)	41.5 (13.7)	45.3 (10.4)	49.7 (10.9)	35.2 (13.6)	.33
Education (% college degree)	50.0	33.2	50.0	66.7	66.7	.76
Income (% >35k/year)	50.0	50.0	50.0	66.7	50.0	.97
Marital Status (% Married)	33.3	33.3	50.0	33.3	16.7	.86
CPD (m/SD)	17.8 (5.7)	16.8 (6.1)	18.3 (5.4)	12.8 (3.2)	19.3 (10.5)	.53
Age Started (m/SD)	15.7 (3.0)	18.7 (5.6)	18.0 (5.1)	20.3 (6.1)	15.7 (2.9)	.38
FTND (m/SD)	3.8 (1.7)	3.8 (1.7)	4.3 (2.2)	4.5 (0.8)	2.7 (1.6)	.39
CO ppm (m/SD)	16.0 (8.3)	17.7 (11.5)	15.8 (6.9)	16.7 (7.2)	17.0 (11.0)	.98
Saliva cotinine ng/ml (m/SD)	297.4 (145.0)	322.3 (170.4)	298.8 (128.9)	249.4 (73.5)	230.1 (107.8)	.66

Note.

CPD = Cigarette per day; FTND = Fagerstrom Test for Nicotine Dependence;

CO = expired carbon monoxide; ppm = parts per million

Table 2

Mean (Standard Deviation) Smoking-related Outcomes by Time-point and E-cigarette Brand

	blu			Green Smoke			V2			White Cloud		
	Day 1	**Day 5**	**Day 10**	**Day 1**	**Day 5**	**Day 10**	**Day 1**	**Day 5**	**Day 10**	**Day 1**	**Day 5**	**Day 10**
Saliva cotinine ng/ml	297.4 (145.0)	101.7 (56.5)	114.2 (64.0)	322.3 (170.4)	176.3 (181.5)	166.4 (184.5)	249.4 (73.5)	113.6 (50.8)	140.5 (121.2)	230.1 (107.8)	123.9 (22.1)	53.8 (3.1)
CO (ppm)	19.2 (9.8)	2.6 (1.9)	3.2 (2.2)	21.6 (8.8)	3.0 (2.0)	4.0 (3.4)	22.0 (8.1)	3.0 (1.9)	4.8 (3.5)	15.5 (3.5)	1.5 (1.4)	1.5 (0.7)
Number of Puffs (Lab Session)	12.8 (3.5)	12.0 (8.0)	11.8 (5.4)	14.2 (4.1)	20.8 (17.0)	10.8 (3.1)	10.8 (2.6)	13.0 (10.2)	14.6 (9.8)	18.0 (5.7)	16.5 (7.8)	16.5 (3.5)
Overall Withdrawal	8.2 (5.9)	6.0 (3.7)	7.0 (4.6)	4.3 (2.6)	7.0 (5.4)	6.5 (4.5)	7.0 (4.8)	10.8 (8.3)	11.0 (5.0)	7.5 (9.2)	10.5 (2.1)	11.0 (5.0)
Overall Craving	34.8 (14.9)	25.2 (7.1)	23.2 (11.4)	33.0 (11.8)	35.6 (16.9)	27.4 (15.4)	33.8 (7.4)	29.2 (10.0)	32.4 (10.2)	38.5 (24.7)	39.5 (21.9)	30.5 (27.6)
Cigarette Liking	610.2 (189.6)	358.8 (142.2)	282.2 (172.1)	685.0 (161.0)	359.0 (105.6)	380.6 (173.1)	628.2 (61.9)	329.4 (123.4)	424.4 (100.4)	584.5 (290.4)	314.5 (55.6)	287.0 (134.4)
Nicotine Effects	43.6 (34.0)	73.4 (59.6)	118.8 (68.6)	140.8 (104.0)	102.4 (142.7)	81.0 (112.1)	51.8 (30.5)	72.8 (61.4)	35.6 (32.1)	58.0 (14.1)	16.5 (9.2)	10.5 (3.5)
Change in Withdrawal	−4.5 (5.5)	−1.2 (4.5)	−3.2 (4.0)	0.4 (7.4)	−4.0 (2.9)	−4.2 (3.4)	−3.7 (2.9)	−1.3 (2.1)	−4.6 (5.4)	−1.5 (4.8)	−4.3 (3.1)	−2.5 (3.5)
Change in Craving	−10.2 (14.3)	−1.8 (7.3)	−4.8 (5.2)	−11.5 (13.8)	−13.8 (19.0)	−7.8 (8.7)	−20.6 (11.6)	−4.8 (7.4)	−10.2 (5.8)	−15.5 (8.0)	−24.63 (13.7)	−7.0 (8.5)

Note.

Day 1 = smoking usual brand; Days 5 and 10 = smoking e-cigarette; CO = expired carbon monoxide