Original investigation

A Pilot Randomized Crossover Trial of Electronic Cigarette Sampling Among Smokers

Ellen Meier PhD¹, Amy E. Wahlquist MS², Bryan W. Heckman PhD^{3,4},
K. Michael Cummings PhD^{2,3,4}, Brett Froeliger PhD^{3,4,5},
Matthew J. Carpenter PhD^{2,3,4}

¹Department of Psychiatry, University of Minnesota, Minneapolis, MN; ²Department of Public Health Sciences, Medical University of South Carolina (MUSC), Charleston, SC; ³Department of Psychiatry and Behavioral Sciences, MUSC, Charleston, SC; ⁴Hollings Cancer Center, MUSC, Charleston, SC; ⁵Department of Neurosciences, MUSC, Charleston, SC

Corresponding Author: Ellen Meier, PhD, Department of Psychiatry, University of Minnesota, 717 Delaware St SE, Minneapolis, MN 55414, USA. Telephone: 612-624-4532; Fax: 612-624-4610; E-mail: meier109@umn.edu

Abstract

Introduction: Electronic cigarette (EC) use is proliferating, but initial uptake patterns and their influence on smoking remains unclear. This study of EC sampling examines naturalistic uptake of ECs, as well as effects on smoking and perceived reward from smoking and vaping.

Methods: Within a double-blind randomized crossover design, smokers ($n = 24$; 75% male; $M_{\text{age}} = 48.5$ years) smoked as usual for 1 week, followed by two counterbalanced naturalistic (ie, *ad libitum* use) weeks of either placebo or active first generation ECs. Vaping and regular smoking was measured daily using diaries and at weekly clinic visits. Perceived reward from ECs and intentions/confidence to quit were also assessed. Analyses compared variables during the naturalistic smoking week and each EC week while controlling for sequence and baseline measurements of respective variables.

Results: No significant differences emerged between active and placebo EC weeks in vaping or regular smoking, EC reinforcement, and intention/confidence to quit smoking. Satisfaction from smoking ($p = .04$) and smoking's ability to reduce cravings ($p = .003$) decreased from the naturalistic to active EC week. Behavioral dependence to cigarettes decreased from the naturalistic ($M = 16.5$, $p = .02$) to active ($M = 14.7$) and placebo ($M = 14.2$) EC weeks.

Conclusions: Few differences emerged in vaping, regular cigarette use, and overall reactions to ECs between active and placebo ECs. Active ECs appeared to decrease reinforcement from smoking, and both active and placebo ECs reduced behavioral dependence to cigarettes. Nicotine (per labeling) may have minimal influence on the uptake of first generation ECs among smokers.

Implications: First generation ECs provide an important behavioral/sensorimotor replacement for cigarettes, regardless of nicotine delivery, but substantial substitution may be minimal when smokers are only asked to use *ad libitum*. However, newer models of EC devices that provide better nicotine delivery should be examined for potential differential patterns of smoking and vaping (eg, decreased smoking and increased vaping) given their suggested greater ability to provide nicotine and behavior/sensorimotor replacement.

Introduction

Electronic cigarettes (ECs) are the fastest growing market trend to affect tobacco use. Within the United States, the most recent national survey indicated that over half (51.1%) of smokers have tried an EC, and approximately 20% have “vaped” in the past 30 days.¹ In 2014, EC sales exceeded \$1 billion,² and each of the three largest US tobacco companies have entered the EC market.³ Although the EC literature is growing, there remains concern about how they will impact public health, including their long-term effects on cigarette use among smokers, appeal to youth and novice smokers, and the effects of long-term vaping on health. Studies examining the safety and utility of these products as an alternative to combustible cigarettes are necessary.

Available evidence suggests ECs are a less harmful alternative to combustible tobacco but that they are not harmless.⁴⁻⁶ Depending on the toxin, ECs emit 1/9 to 1/450 the level of toxicants as combustible cigarettes.⁷ Results from a small-scale study suggest that toxicant exposure is reduced when smokers switch to ECs, but still dual use combustible tobacco.⁸ ECs may be a viable reduced harm alternative for smokers who are able to switch from their combustible cigarettes. For example, smokers who switched from combustible cigarettes to an EC showed significant reductions in exposure to carbon monoxide (CO) and acrolein.⁸ Similarly, a retrospective analysis of asthmatic smokers showed significant improvements in asthma control after switching from combustible cigarettes to ECs.⁹ However, whether smokers are able to effectively switch to ECs is unclear as most published studies examining the effects of EC use on smoking behaviors are either (1) lab-based, (2) cross-sectional online studies of prevalence and predictors of use, (3) among current EC users, and/or (4) are comparison rather than controlled studies.^{10,11}

Only three published randomized controlled trials (RCT) have examined the effects of first generation EC use on smoking behavior. Across these studies, instructions for use and nicotine content were differentially manipulated, both of which could independently influence patterns of use. In regards to instructions, each study reportedly asked smokers to use ECs as they would like (eg, naturalistic); however, one study encouraged participants to reduce their smoking by at least 50%¹² and another encouraged participants to begin using the EC 1 week prior to their quit date.¹³ Both smokers interested^{12,13} and uninterested in quitting/reducing smoking,¹⁴ displayed similar smoking cessation rates regardless of instructions. In regards to nicotine content, one study found that smokers provided nicotine-containing EC (eg, active EC) displayed significantly greater reductions in smoking than those provided a nicotine-free EC (eg, placebo EC).¹² Collectively, current research is inconclusive as to how patterns of use are influenced by (1) instructions for use (eg, *ad libitum* vs. reduction/quitting), and (2) nicotine (ie, psychopharmacological properties) versus non-nicotine factors (eg, behavioral/sensorimotor).¹⁵ Additionally, only one study mentioned above examined the differential impact of nicotine on EC and combustible cigarette use in a truly naturalistic (eg, no instructions to reduce or quit smoking), among smokers uninterested in quitting.¹⁴ Most smokers are uninterested in quitting¹⁶ and those who begin EC use likely do so with minimal use instructions. Therefore, it is important to examine factors, such as the effect of nicotine content, under naturalistic instructions among this subpopulation.

The current study is a randomized crossover trial in which smokers uninterested in quitting were provided an active and placebo EC across 2 weeks to sample as they like (1 week per product). The present study aims to assess (1) patterns of EC and combustible

cigarette use, as compared to a preceding naturalistic smoking week, (2) effects of EC sampling on perceptions of smoking and vaping, and (3) the differential effects of active versus placebo ECs on the above aims. It was hypothesized that smokers would decrease their combustible cigarette use while dual using ECs, with greater reductions during the active EC week. Secondly, it was hypothesized that EC would effectively decrease craving and withdrawal from combustible cigarettes, with the active EC providing greater relief. This exploratory study examines how smokers use and perceive ECs when provided an opportunity to sample them, as well as the influence of nicotine exposure on use and perceptions.

Method

Design

This study was a double-blind randomized crossover design in which participants first smoked as usual for 1 week, followed by 2 counterbalanced weeks of either placebo or active ECs (four lab visits over three consecutive weeks). This design allowed the assessment of whether ECs altered one's smoking patterns as compared with naturalistic smoking and to determine if this effect was nicotine-specific. Participants completed daily written diaries of their EC and regular cigarette use providing “real time” assessment of actual use as opposed to retrospective assessment of past week use. Additionally, during visits 2–4, participants completed a smoking resistance task¹⁷ for which smokers were required to demonstrate 12-hour abstinence from all tobacco. Results of the lapse procedures are not presented herein, since most participants achieved maximal duration during the task.

Participants

Participants were 24 adult (≥ 18 years old), daily smokers, (≥ 10 cigarettes per day), not interested in quitting in the next 30 days, recruited from the general community. Eligibility criteria included (1) English speaking, (2) not using cessation medications, (3) interested in using an EC, (4) no use of ECs in the last 6 months, (5) exhaled CO ≥ 6 ppm, (6) no history of cardiovascular trauma or uncontrolled hypertension, and (7) not pregnant, verified by urine pregnancy test.

Procedures

Participants were recruited via local media outlets (eg, Craigslist, radio and print advertisements, and hospital website) and first completed a phone screening to assess eligibility. Interested and eligible participants were scheduled for their first of four visits (baseline), during which they were further screened for eligibility (pregnancy, CO test) and provided informed consent. Baseline questionnaires assessed demographics, smoking history, previous EC use (eg, number of days used and time since last use) and psychological variables related to smoking (eg, craving). Participants also provide a urine sample for cotinine analysis. Participants then scheduled their second visit for 1 week later and were instructed to smoke their cigarettes as they normally do for the next week (naturalistic comparison week). During the naturalistic comparison week, and each of the subsequent EC sampling weeks, participants kept a written diary of their combustible cigarette (and EC) use.

At visit 2 (end of naturalistic week), participants completed CO, provided a urine sample, were assessed for any adverse events, and completed questionnaires. Participants were randomized to receive either an active or placebo EC first and provided with free EC

supplies for 1 week. The product is described further below. Daily diaries persisted as above, now inclusive EC use questions.

Visit 3 (end of first EC week) was identical to visit 2, except participants were provided an alternate EC dose (active vs. placebo), with equivalent instructions. Visit 4 concluded the study, at which time all assessments and biomarkers were collected. No further ECs supplies were provided.

Participants received monetary compensation at each visit in addition to bonuses for compliance with study procedures: \$20–25 per visit, \$1 per day bonus for each smoking diary day, \$50 bonus for completing all four visits in a timely manner. All procedures were approved by the university's institutional review board. No support was provided by the tobacco or EC industries.

Measures

Use of ECs and Cigarettes

Use of ECs (visits 3 and 4 only) was measured using written diaries for each of the 21 days of the study. Daily diaries provided the following variables (1) number of EC puffs per episode of use (eg, "When you did use the e-cigarette yesterday (for each time you pulled it out of your pocket/purse/storage spot), about how many puffs did you take on average?"), (2) number of EC episodes (eg, "how many times did you pull it out of your pocket?"), (3) total EC puffs per day (eg, "Altogether, how many total puffs do you think you took of the e-cigarette yesterday?"), and (4) percent of participants using the EC ≥ 6 days per week. Compliance with the diaries was 97.9% with no more than 2 days missed per participant. Number of cigarettes smoked per day and quit attempts lasting ≥ 7 days were assessed using a Timeline Follow-Back (TLFB) questionnaire at each visit. Participants' Heaviness of Smoking Index (HSI) was calculated using cigarettes per day (CPD) + time to first cigarette (scale 0—no dependence to 6—high dependence).¹⁸

Withdrawal

The nine-item Minnesota Nicotine Withdrawal Scale¹⁹ was used to assess smoking related craving and withdrawal symptoms (eg, anxiety, restlessness) at each visit ($\alpha = 0.65$). Responses ranged from 0 (none) to 4 (severe). Average scores across all items were used for analyses as recommended.²⁰

Physical Dependence

Participants completed the 37-item Brief Wisconsin Inventory of Smoking Dependence Motives (B-WISDM) to assess level of tobacco dependence at baseline.²¹ Responses to items range from 1 (not true of me) to 7 (extremely true of me). The mean score of this measure was examined.

Behavioral Dependence

Participants completed the Glover-Nilsson Smoking Behavioral Questionnaire,²² an 11-item measure asking participants to rate how much they value their cigarette habit and the ritual of smoking on a scale of 0 (not at all) to 4 (extremely). Items also assessed frequency of experiencing environmental triggers for smoking on a scale of 0 (never) to 4 (always). This measure is a valid and reliable assessment ($\alpha = 0.74$) of behavioral dependence and has divergent validity with the Fägerstrom Test for Nicotine Dependence.²³ Total scores <12 indicate mild behavioral dependence, 12–22 = moderate, 23–33 = strong, and >33 = very strong. This measure was completed during at each visit.

Perceived Reward

Participants completed perceived reward of smoking measures at each visit and twice during visits 3 and 4—once for smoking and again for vaping. The modified Cigarette Evaluation Scale²⁴ contains 12 items assessing likability and acute effects (eg, "Did smoking/vaping make you dizzy?") on a scale of 1 (not at all) to 7 (extremely). This measure comprises five subscales; specifically, smoking/vaping satisfaction, psychological reward, aversion, enjoyment of respiratory track sensations, and craving reduction (cigarette version $\alpha = 0.86$; EC version $\alpha = 0.94$).

Intention and Confidence to Quit

Intention to quit in the next month and confidence to quit now were each assessed with 0 (definitely no/not at all confident) to 10 (definitely yes/extremely confident) visual analog scales at each visit. These were administered twice at each visit, first in reference to "cigarette smoking" and subsequently in reference to "all tobacco products, including e-cigarettes." Intentions/confidence in quitting both combusted cigarettes and ECs were assessed in order to understand the role of ECs in nicotine addiction, including possibly to ECs, more broadly.

Biochemical Assessment

Exhaled CO was measured at all visits. Urine samples were obtained at each visit for analysis of total cotinine.

Products

Participants were given a BluCig starter kit with up to seven cartridges (prefilled, with either active 16 mg or 0 mg nicotine solution). In a previous lab-based study, most smokers used three cartridges of this same device per week, with a maximum of seven; therefore seven cartridges were dispensed to provide a sufficient supply for the sampling weeks.²⁵ Participants and research staff conducting sessions were blinded to dose. All cartridges were pre-loaded by the manufacturer. Labeling was removed by a research team member not involved in participant contact to mask placebo versus active ECs. We restricted flavor options to regular tobacco flavor or menthol to most closely match usual cigarette brand flavor profile and reduce unwanted variance in product.

Participants were instructed "this e-cig may or may not contain nicotine; we ask that you try it at least once, but use it however you like; smoke regular cigarettes as you wish." Participants were shown how to charge the device and sampled the product during the visit. Additionally, they were provided a handout on how to use the product (eg, switching cartridges) and general information about ECs.

Data Analysis

Analyses were conducted using SAS software, Version 9.3 of the SAS System for Windows (Copyright 2002–2010 SAS Institute Inc., Cary, NC) and SPSS, version 20 (IBM Corp, Armonk, NY). Descriptive statistics were used to examine the sample at baseline. Baseline demographic, tobacco use history, and baseline dependence levels were examined. Daily diary data were collapsed to provide weekly averages. Generalized linear mixed models were conducted comparing study weeks (naturalistic vs. active EC vs. placebo EC) while controlling for each dependent variable's baseline measurements (when available) and sequence (active/placebo or placebo/active). Some variables were not assessed during the naturalistic or baseline sessions, and therefore, only active versus placebo EC comparisons

were made. Results were considered significant at $p < .05$. Cohen's d was calculated for all between group analyses.

Results

Sample Characteristics

A demographic and tobacco use history summary is presented in Table 1. Participants' mean age was 48.5 ($SD = 11.3$) years. Most participants were male (75%). The sample consisted of a near even distribution of self-reported white (54.2%) and non-white participants (45.8%). Mean CPD was 16.3 ($SD = 6.7$), and 33.3% of the sample had previously tried an EC. Of those who reported previously trying an EC, the average length of EC use was 3.6 days ($SD = 4.7$; range = 1 hour to 2 weeks) and it had been an average of 9.4 months ($SD = 5.9$ months) since they last used an EC.

Use of Cigarettes and ECs

Results from regular cigarettes and EC use models across the naturalistic and EC conditions are shown in Table 2. One participant

quit smoking during the study. This individual's sampling sequence was active first, placebo second, and with smoking abstinence occurring during the placebo EC week. Overall, there were no significant differences in CPD between the naturalistic and EC conditions, nor between the active and placebo EC conditions. Baseline CPD was the only variable that predicted subsequent CPD. Number of EC puffing episodes per day ($p = .65$), number of puffs/episode ($p = .75$), total EC puffs/using day ($p = .80$), and number of days using EC/wk ($p = .62$) did not differ between active and placebo EC conditions. All effect sizes were small to medium ($d = 0.04$ – 0.44) and are shown in Table 3.

Withdrawal

There were no significant group differences between the naturalistic, active EC, and placebo EC conditions on Minnesota Nicotine Withdrawal Scale scores ($p = .27$). Self-reported withdrawal ($p < .001$) at baseline was predictive of withdrawal at successive visits (see Table 2 for complete data). All effect sizes were small ($d = 0.09$ – 0.37) and are shown in Table 3.

Behavioral Dependence

There was a significant decrease in self-reported behavioral dependence ($p = .02$) from the naturalistic smoking condition ($M = 16.5$, standard error [SE] = 0.8) to both of the EC conditions ($M_{\text{active}} = 14.7$, $SE = 0.8$; $M_{\text{placebo}} = 14.2$, $SE = 0.8$), with no differences between EC conditions. Baseline behavioral dependence was also a significant predictor of subsequent dependence in the model ($p < .0001$; see Table 2). Decreases in behavioral dependence demonstrated medium effect sizes ($d = 0.49$ – 0.62) from naturalistic to EC weeks, and a small effect size between EC weeks ($d = 0.13$).

Perceived Reward

Participants' perceived reward from vaping and smoking regular cigarettes as measured by the modified Cigarette Evaluation Scale are in Table 2. There were significant differences between study conditions on reported satisfaction experienced from smoking regular cigarettes ($p = .04$) and ability to reduce cravings ($p = .003$). Participants' self-reported satisfaction from smoking was higher during the naturalistic condition ($M = 4.51$, $SE = 0.3$) than during the active EC condition ($M = 3.99$, $SE = 0.3$; $d = 0.39$), as was the effects of smoking on craving reduction ($M_{\text{naturalistic}} = 5.3$, $SE = 0.3$ vs. $M_{\text{active}} = 4.61$, $SE = 0.3$; $d = 0.54$). Modified Cigarette Evaluation Scale scores for smoking during the EC placebo condition did not differ from the naturalistic or active EC conditions. In regards to the modified Cigarette Evaluation Scale scores for ECs, participants reported no differences between the active and placebo ECs.

Intention and Confidence to Quit

Results of the models examining participants' intention/confidence to quit smoking cigarettes and all tobacco products are in Table 2. There were no significant differences between naturalistic, active EC, and placebo EC conditions on intention to quit smoking ($p = .75$) or to quit all tobacco products ($p = .11$), in the next month. There were also no significant difference between conditions on confidence to quit smoking cigarettes ($p = .38$) or all tobacco products ($p = .40$) now. Baseline intention and confidence to quit were significantly related to the outcomes in each model ($ps .002$ to $<.001$). All effect sizes were small ($d = 0.2$ – 0.19) and are shown in Table 3.

Biochemical Assessment

Exhaled CO and serum cotinine (controlling for baseline cotinine and sequence) levels are in Table 2. There were no significant

Table 1. Baseline Demographics and Smoking Characteristics

Variable	<i>M</i> (<i>SD</i>) or <i>n</i> (%)
Age	48.5 (11.3)
Gender, male	18 (75.0%)
Race	
White	13 (54.2%)
Black or African American	11 (45.8%)
Hispanic	0
Employment status, full-time	5 (20.8%)
Education ^a	
Some high school	1 (4.2%)
High school graduate or GED	9 (37.5%)
Some college	9 (37.5%)
College graduate or more	4 (16.7%)
Annual household income	
Less than \$25K	10 (41.7%)
\$25–\$50K	9 (37.5%)
More than \$50K	2 (8.3%)
Unsure/refused	3 (12.5%)
Cigarettes per day	16.3 (6.7)
Age of daily smoking onset	16.8 (4.6)
Number of lifetime quit attempts	5.0 (7.5)
Minutes to first cigarettes	
<5 min	5 (20.8%)
6–30 min	15 (62.5%)
31–60 min	4 (16.7%)
>60 min	0
Brief WISDM	43.9 (11.93)
HSI	2.9 (1.2)
Tried ECs before	33.3%
Duration of EC use in days	3.6 (4.7)
Months since last EC use	9.4 (5.9)
Exhaled carbon monoxide (CO)	31.1 (13.1)
GNSBQ (Behavioral Dependence)	13.5 (4.2)

GNSBQ = Glover-Nilsson Smoking Behavioral Questionnaire; HSI = Heaviness of Smoking Index, 1–2 very low dependence, 3 = low to moderate dependence, 4 = moderate dependence, 5+ = high dependence; WISDM = Brief Wisconsin Inventory of Smoking Dependence Motives.

^aPercentages do not add to 100% due to missing data.

Table 2. Results of General Linear Mixed Models Examining Smoking, Vaping, and Self-reported Effects During Naturalistic and EC Weeks

Variable	Naturalistic week, M (SE)	Active EC week, M (SE or CI)	Placebo EC week, M (SE or CI)	Study week (naturalistic vs. active vs. placebo) <i>p</i>
Smoking and vaping				
Cigs/d	14.1 (1.0)	12.2 (1.0)	12.0 (1.1)	.14
# EC puffing episodes/ using day ^a	—	6.3 (1.1)	5.7 (1.1)	.65
# Puffs/episode	—	6.3 (1.2)	6.5 (1.2)	.75
Total EC puffs/using day ^a	—	25.1 (3.8)	24.5 (3.9)	.80
# Days using EC/wk ^b	—	5.3 (0.4)	5.5 (0.4)	.62
% Regular EC use (≥6 d)	—	70% (±18.3)	40% (±19.6)	.66
Carbon monoxide	11.4 (1.3)	11.6 (1.3)	10.2 (1.3)	.57
Cotinine	1123.9 (108.2)	1190.1 (110.6)	992.1 (110.3)	.11
Subjective effects				
MNWS	1.08 (0.1)	0.90 (0.1)	0.84 (0.1)	.27
GNSBQ (Behavioral Dependence)	16.5 [†] (0.8)	14.7 [†] (0.8)	14.2 [†] (0.8)	.02*
mCEQ—smoking				
Satisfaction	4.51 [†] (0.3)	3.99 [‡] (0.3)	4.28 ^{†‡} (0.3)	.04*
Psych reward	3.99 (0.2)	3.59 (0.2)	3.64 (0.2)	.16
Aversion	1.58 (0.1)	1.47 (0.1)	1.44 (0.2)	.65
Throat sensations	3.59 (0.3)	3.09 (0.3)	3.24 (0.3)	.09
Craving reduction	5.3 [†] (0.3)	4.61 [†] (0.3)	4.95 ^{†‡} (0.3)	.003**
mCEQ—EC				
Satisfaction	—	3.49 (0.3)	3.18 (0.3)	.17
Psych reward	—	2.38 (0.2)	2.36 (0.2)	.93
Aversion	—	1.24 (0.1)	1.15 (0.1)	.15
Throat sensations	—	2.68 (0.2)	2.58 (0.2)	.66
Craving reduction	—	2.92 (0.3)	2.87 (0.3)	.88
Intention to Quit smoking	53.5 (4.2)	57.6 (4.4)	55.5 (4.4)	.75
Intention to Quit all tobacco	42.5 (3.9)	51.6 (4.1)	53.5 (4.1)	.11
Confidence to Quit smoking	44.9 (4.8)	48.8 (5.0)	52.9 (5.0)	.38
Confidence to Quit all tobacco	41.6 (4.9)	46.6 (5.1)	49.2 (5.0)	.40

CI = confidence interval; EC = electronic cigarette; GNSBQ = Glover-Nilsson Smoking Behavioral Questionnaire; mCEQ = modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; SE = standard error. Non-alike superscripts denote pairwise differences ($p < .05$). Variables without any superscripts denote all group differences were nonsignificant ($p > .05$).

^aExcludes days of nonuse.

^bAll participants used the EC at least once per week.

* $p < .05$; ** $p < .01$.

differences between study conditions in CO ($p = .57$) or cotinine levels ($p = .11$). Baseline cotinine was a significant predictor of cotinine at subsequent measurements ($p = .001$); however, baseline CO did not predict subsequent CO measurements ($p = .07$). All effect sizes were small ($d = 0.03$ – 0.38) and are shown in Table 3.

Discussion

Within this small-scale crossover study of active versus placebo ECs, smokers did not appear to change their smoking behaviors when provided a first generation EC, regardless of whether it did or did not contain nicotine. Smokers vaped on most days of the sampling week; however, substitution was minimal. Although an earlier study by Caponnetto and colleagues¹⁴ observed a decrease in smoking and exhaled CO over a longer sampling period (eg, 1 year), this previous study also observed no differences in CO between smokers provided active or placebo ECs. Similarly, in a small lab study in which smokers were provided an active EC to sample for a week, smokers reduced their CPD by 44% during a 1-week sampling period of *ad libitum* use.²⁵ Additionally, smokers reported an increase in readiness and confidence to quit smoking. Unlike the current study, Wagener and colleagues²⁵ allowed participants to sample three different ECs in the lab (ie, SmokeTip, ProSmoke, and BluCig), selecting one as their preferred

product to use over a subsequent sampling week. BluCig was selected more often than the other two brands. Collectively, practice with the product and/or longer sampling periods than 1 to 2 weeks may result in greater smoking reductions than seen in the current study.

Compared to the naturalistic week, smokers in this study reported no change in withdrawal symptoms during active and placebo EC weeks, which given the minimal changes in cigarette smoking observed and the overnight abstinence requirement, would be expected. In contrast, smokers' self-reported behavioral dependence to cigarettes decreased from the naturalistic week to the active and placebo weeks. Maintenance of withdrawal levels, but changes in behavioral dependence during the placebo week suggests that EC use may be reinforced by its ability to provide a behavioral replacement rather than nicotine replacement. It is important to note that the lack of differences between placebo and active ECs could be due to the model of ECs used in the current study—BluCig. Although BluCig is the second largest selling EC brand,²⁶ first generation ECs may not provide as much relief from withdrawal as second generation tank system ECs,²⁷ likely because of more efficient nicotine delivery from tank devices.²⁸ It will be important for future research to further explore product substitution among different EC devices, while still parsing whether such substitution is nicotine-specific versus behaviorally driven.

Table 3. Effect Sizes of General Linear Mixed Models

Variable	Naturalistic vs. active effect size	Naturalistic vs. placebo effect size	Active vs. placebo Cohen's <i>d</i> or OR
Smoking and vaping			
Cigs/d	0.39	0.44	0.05
# EC puffing episodes/ using day	—	—	0.11
# Puffs/episode	—	—	0.05
Total EC puffs/using day	—	—	0.04
# Days using EC/wk	—	—	0.12
% Regular EC use (≥6 d)	—	—	OR = 1.34
Carbon monoxide	0.03	0.19	0.22
Cotinine	0.12	0.25	0.38
Subjective effects			
MNWS	0.28	0.37	0.09
GNSBQ (Behavioral Dependence)	0.49	0.62	0.13
mCEQ—Smoking			
Satisfaction	0.39	0.17	0.22
Psych reward	0.35	0.31	0.04
Aversion	0.15	0.19	0.04
Throat sensations	0.31	0.22	0.10
Craving reduction	0.54	0.28	0.27
mCEQ—EC			
Satisfaction	—	—	0.26
Psych reward	—	—	0.02
Aversion	—	—	0.23
Throat sensations	—	—	0.10
Craving reduction	—	—	0.03
Intention to Quit smoking	0.15	0.02	0.17
Intention to Quit all tobacco	0.04	0.19	0.16
Confidence to Quit smoking	0.16	0.34	0.17
Confidence to Quit all tobacco	0.21	0.32	0.11

EC = electronic cigarette; GNSBQ = Glover-Nilsson Smoking Behavioral Questionnaire; mCEQ = modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; OR = odds ratio.

Compared to the naturalistic week, ratings of the satisfaction experienced from smoking regular cigarettes and the ability of smoking to reduce cravings were lower, but only when smokers used the active EC. These results were not replicated during the placebo EC week; therefore, the reinforcing effects of smoking may be reduced slightly when smokers are provided both a behavioral and nicotine replacement. This is consistent with previous research demonstrating that smokers rate cigarettes as less rewarding when they are provided with an active nicotine patch versus a placebo patch.²⁹ Additionally, second generation ECs have been shown to be equally as reinforcing as a cigarette.³⁰ This could also demonstrate the potential for dependence to shift from cigarettes to ECs, a less harmful substitute.³¹ It is possible that with longer sampling or stronger/more advanced EC devices, greater conversion to EC would be observed; however, future research is needed to determine whether this would happen.

Several limitations of this study are worth noting. First, the duration of the sampling period was only 1 wk/EC, limiting the amount of time participants had to establish vaping behaviors. Previous studies in which smokers demonstrated greater substitution with first generation ECs had longer follow-up periods (eg, 3 weeks to 1 year).^{12,14} It is possible that longer sampling periods would have resulted in more established vaping patterns, differential use patterns between the active and placebo ECs, and/or decreases in smoking over time. Second, given that an overnight abstinence protocol was employed at the naturalistic, active, and placebo ECs weeks, true withdrawal symptoms as a result of vaping are more difficult to determine. Third, the study was restricted to a small number of smokers who

were uninterested in quitting in the next 30 days limiting the generalizability of results to all smokers, particularly to those who may try an EC with intentions of reducing or quitting combustible cigarettes. Despite the small sample size, nonsignificant differences appeared to reflect low effect sizes rather than a lack of power. Fourth, 33% of the sample had previous experience with ECs potentially influencing their behaviors and perceptions. Future research with larger sample sizes examining how this experience may influence uptake behaviors is needed. Fifth, paper diaries were utilized for the present study potentially allowing participants to complete diaries in one sitting rather than on a daily basis as instructed. These limitations are offset by study strengths including a randomized, crossover design with focus on short-term naturalistic use.

In conclusion, while there were few differences in cigarette use and responses to the EC between the placebo and active ECs, the reinforcing effects of smoking (eg, smoking satisfaction and the ability for cigarettes to reduce cravings) were attenuated slightly during active EC weeks. Smokers also reported a decrease in behavioral dependence to smoking from the naturalistic week to the EC weeks. The present study provides further information as to whether ECs can serve as an effective substitute for smoking, as most smokers dual used the placebo/active EC and regular cigarettes. Collectively, this suggests that first generation ECs provide an important behavioral/sensorimotor replacement for cigarettes, regardless of nicotine delivery, but that substantial substitution may be minimal when smokers are only asked to use *ad libitum*. Newer models of EC devices that provide better nicotine delivery may result in different patterns of smoking

and vaping (eg, decreased smoking and increased vaping) given their suggested greater ability to provide nicotine and behavior/sensorimotor replacement. Future longitudinal research is needed to investigate the role ECs have in substitution, particularly as EC devices advance.

Funding

Research reported in this publication was supported by grants P01 CA138389, P30 CA138313 (Hollings Cancer Center Support Grant) from the National Cancer Institute of the National Institutes of Health and UL1 TR000062 from the National Center for Advancing Translational Science of the National Institutes of Health. BWH was supported by K12DA031794. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Declaration of Interests

KMC has received grant funding from the Pfizer, Inc., to study the impact of a hospital-based tobacco cessation intervention. He also receives funding as an expert witness in litigation filed against the tobacco industry. We have no other declarations of interests to declare.

Acknowledgments

The authors would like to acknowledge the work of the many research assistants who contributed to the conduct of this study, primarily Amy Boatright, Nichols Mabry, and Caitlyn Hood.

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