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Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Naturalistic, Randomized Pilot Trial of E-Cigarettes: Uptake, Exposure, and Behavioral Effects

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Abstract

Background: Most studies of electronic nicotine delivery systems (ENDS) compare self-selected users versus nonusers. The few randomized studies to date generally support a positive impact on reducing smoking behavior, but these studies are focused on guided ENDS use. This study presents a randomized, naturalistic trial of ENDS with prospective outcomes of uptake and behavioral changes in smoking.

Methods: Adult smokers with minimal ENDS history were randomized in a 2:1 ratio to receive product for 3 weeks ($n = 46$), or not ($n = 22$). Changes in nicotine delivery (16 vs. 24 mg), midway through the study allowed a compelling opportunity to examine two ENDS products compared with the control group. Primary outcomes, assessed via daily diaries during sampling period and in-person laboratory visits over 4 months, included uptake and usage of ENDS, cessation-related outcomes, and exposure to smoke constituents.

Results: All ENDS participants tried product at least once, with 48% of 24 mg and 30% of 16 mg using their assigned product for the entire sampling period. Within the 24 mg ENDs group, 57% made an independent purchase of ENDS, versus 28% of 16 mg, and 14% of control participants ($P = 0.01$). Smokers in both ENDS groups significantly reduced their smoking, whereas control participants did not ($P = 0.03$). Cessation behaviors (quit attempts, biologically verified abstinence) numerically but not statistically favored ENDS participants.

Conclusions: Results suggest that cigarette smokers are willing to use ENDS with trends toward reduced cigarette smoking and positive changes in cessation-related behaviors.

Impact: Randomized, naturalistic trials such as presented herein are needed to understand the population impact of e-cigarettes. *Cancer Epidemiol Biomarkers Prev; 26(12); 1795–803. ©2017 AACR.*

Introduction

The proliferation of electronic nicotine delivery systems (ENDS, or e-cigarettes) has generated a rapidly growing yet divergent literature on how these products impact smoking behavior (1, 2). Most studies that assess the impact of ENDS on smoking are either cross-sectional or observational cohort designs (3, 4). Evidence suggests that the majority of ENDS users have intention to reduce and/or quit smoking (5), and a range of studies have shown ENDS use to be associated with quit attempts (6), reduction and/or cessation (7–16). More recent cohort studies further document a positive association between use and subsequent quitting (17, 18), particularly when ENDS are used regularly (19–21). However, not all studies have been consistent, and some have shown negative associations with quitting (22–25). The rapidly evolving marketplace combined with methodological constraints across studies likely contributes to inconsistent findings, making it difficult to draw firm conclusions about the value of ENDS as a smoking cessation method. A major barrier to study interpretation, especially from observational studies, is the reliance on self-selected samples of users versus nonusers. This self-selection bias presents challenges when determining causal inferences with regard to ENDS and their impact on smoking behavior.

A more direct test of the impact of ENDS comes through randomized controlled trials. Only four such trials exist (26–29) and two are pending (30, 31). All but one of the existing RCTs were based on early-generation products. The first was a study of Italian smokers (27); randomized smokers ($N = 300$); and high, moderate, or placebo ENDS. Rates of abstinence after 3 months (11%, 17%, 4% in each group, respectively) and 12 months (13%, 9%, 4%) suggested higher quit rates among active ENDS groups. The second study, a noninferiority, cessation-focused trial ($N = 657$), came from New Zealand (28, 32). Smokers were randomized to receive (i) an early-generation ENDS product, (ii) transdermal patch, or (iii) placebo ENDS. Abstinence rates numerically but not statistically favored the ENDS product over

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both the nicotine patch and placebo. The third study was a small-scale ($N = 48$), randomized trial from Belgium that showed short-term (2-month) increases in quitting as a function of newer-generation ENDS, which dissipated over longer-term (8 months) follow-up (26). Finally, a recent reduction-focused trial demonstrated significant decreases in smoking as compared among active versus placebo ENDS (29).

Most of the aforementioned trials focused on prescribed and/or structured e-cigarette use, that is, to reduce and/or quit smoking, which is entirely different from real-world uptake. Naturalistic provision of ENDS, yet still within a randomized design, allows for assessment of self-determined use and its causal impact on downstream smoking behavior while avoiding biases of self-selection inherent in the observational studies. We have previously used the naturalistic, randomized clinical trial framework to evaluate uptake, patterns, and consequences of nicotine products, both snus (33) and cessation pharmacotherapies (NRTs; 34, 35), and now extend this design to ENDS.

The current study presents results from a pilot ($N = 68$) test of short-term (3 weeks) ENDS sampling versus not, with follow-up for an additional 3 months (clinicaltrials.gov identifier: NCT02357173). Our general aim was to approximate the real-world scenario in which smokers are exposed to e-cigarette and decide on their own if and how they will use them. Our specific focus was on: (i) uptake and usage of the ENDS product during the sampling period and beyond, (ii) smoker evaluation of the product, (iii) changes in smoking and cessation-related outcomes, and (iv) differences in exposure to cigarette smoke constituents (i.e., cotinine, carbon monoxide, and NNAL).

Materials and Methods

Participants

Nontreatment seeking smokers were recruited from the local community (southeastern U.S. urban area; approximately 30% nonwhite) using various media outlets. To be eligible, participants were required to be/have: (i) age 18+, (ii) current smoker of $\geq$5 cigarettes per day (CPD) for $\geq$1 year, (iii) no recent history of cardiovascular distress (heart attack in past 3 months, arrhythmia, uncontrolled hypertension), (iv) neither pregnant nor breastfeeding (verified), (v) absence of any major current psychiatric impairment, (vi) current, active use of email, (vii) at least some concern for health effects of smoking (>none at all on a Likert scale), and (viii) not used any ENDS product in the past 6 months, and (ix) never purchased an ENDS product. The latter two criteria were meant to ensure a study sample that was relatively naïve to ENDS so we could more accurately gauge how the provision of the product in this study impacted use of the product and smoking behaviors.

Participants eligible during phone screen were assessed and ultimately consented during the initial in-person laboratory visit. Randomization to group was stratified by motivation to quit in the next 30 days (0–6 vs. 7–10 on a VAS scale) but proportioned 2:1 (ENDS:control) to increase precision estimates for e-cigarette uptake and usage. The study consisted of two phases. An initial 3-week sampling period allowed participants to use ENDS (or not), complete ecological momentary assessment (EMA; 3x daily) throughout, and visit the laboratory at weeks 2, 3, and 4. At week 4, daily EMA discontinued and no further product was offered. The 3-month follow-up period consisted of laboratory visits at weeks 8, 12, and 16. Study flow is depicted in Fig. 1.

Participants were compensated up to $346, inclusive of EMA-contingent reimbursement. Control participants, not offered ENDS, were offered an additional $30 to compensate for the free product given to the ENDS group. All procedures were approved by our local institutional review board (IRB) in accordance with recognized ethical guidelines. Written informed consent was obtained from all participants. Data collection began in November 2014 and continued through final follow-up in May 2016.

ENDS

Recent evidence suggests that newer-generation products based on tank systems are better substitutes for cigarettes, as opposed to standard cartridge or ciga-like design products (21). However, at the time of study design, tank systems were just emerging on the market. We also believed that new converts to ENDS would likely start out with a standard cartridge design product instead of a tank system, particularly in the United States where cartridge systems are widely available and advertised in convenience stores. We thus chose BluCig to use in our study which at the time of study onset was the most popular product on the market (36). Also, our earlier work that showed consumer preference for BluCig among other ciga-like devices (37).

We offered ENDS group participants the choice of either traditional tobacco or menthol flavor (other flavors available but not offered to minimize methodological variance) Blu Starter Pack, with 16 mg/mL nicotine (the highest dose available at study initiation). Midway through the study, the manufacturer of Blu altered the product and discontinued availability of the device, replaced with BluPlus+, with 24 mg/mL nicotine, again offered in both tobacco and menthol flavorings, and with improved battery duration (4-watt battery for both devices). In all, 25 participants (54%) received the Blu Starter Pack (16 mg), and 21 participants (46%) received BluPlus+ (24 mg); no switches were made within participants. The change in product (IRB approved) allowed us the unexpected opportunity to assess what impact, if any, the change in product design had on study outcomes. Note that the manufacturer, style of device, and packaging did not change, nor did our messaging to participants. The only difference was the strength of product. Thus, trial outcomes are reported across three groups: control versus 16 mg versus 24 mg ENDS.

We selected a 3-week sampling period for three reasons. First, we believed that smokers who adopt a new product are likely to have a period of acclimation, in which they determine (i) if they like it, and (ii) how to use it to manage cravings. Second, we wanted a sufficiently long-time period to capture the "bookends" of this acclimation period, inclusive of initial trial and established use. Third, this period allowed sufficient time to observe naturalistic changes in cigarette smoking. Participants were given up to seven cartridges at each of three weekly visits (BL, visits 2 & 3) during the sampling period. We purposefully oversupplied product because we did not want to artificially suppress substitution. ENDS group participants were allowed to retain any unused product after the sampling period.

Instructions on usage were kept minimal to preserve naturalistic intent. We simply suggested that ENDS could be used "as you wish, to cut down or quit smoking, help manage smoking restrictions, or both. It is entirely up to you if and how you use this product." We provided participants with materials from the manufacturer marketing, including messaging of (i) no ashes, (ii) odorless, (iii) no after smell, and (iv) made in the United States.

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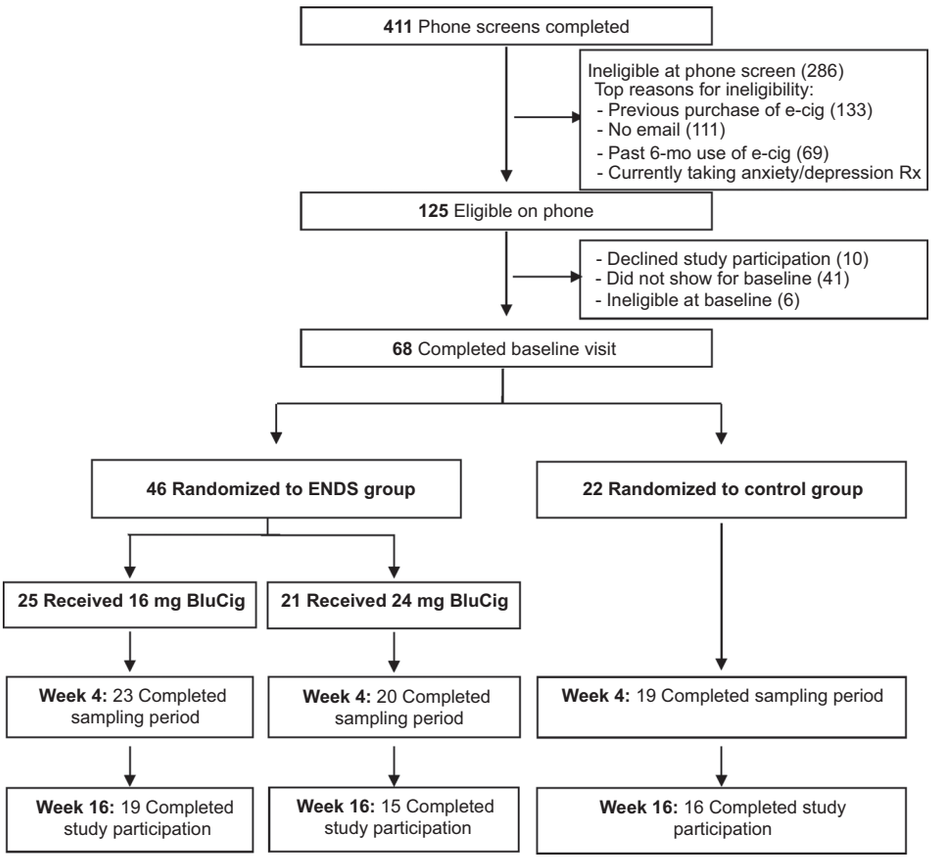

Figure 1.
Participant flow and study retention rates.

Assessments are structured across the four major outcomes noted above

Uptake and usage of ENDS. We adapted EMA methods from prior literature (38). Through our secure, encrypted, online database (REDCap), we preprogrammed and auto-sent an email (or text message reminders to check email) on designated diary days (all 21 days of sampling period). Participants opened a link within the email which took the user to a brief (2–5 minutes) survey, directly entered into REDCap. Participants were "pinged" 3x daily, at semi-random intervals. Validation checks were embedded within each session to protect against rote responding (e.g., "enter 4 here"); sessions with invalid data (2%) were removed from analyses. Within each EMA session, participants were asked about products used in the past hour (electronic, conventional, both or none). If both products were used, the participant was asked to reference the most recent. Setting and context were asked for each conventional/electronic cigarette episode. We used the final EMA entry of each day to assess both (i) number of e-cigarette puffing episodes and (ii) number of cigarettes smoked that day. Both measures thus reflect partial days, which we deemed more feasible than asking number of puffing episodes during a prior day (there is yet no established method for EMA assessment of ENDS). Participants were compensated for compliance (up to $6 per day for 21 days + $10 bonus for ≥80% EMA compliance). Overall compliance was modest but no different across groups: 58% of all EMA sessions completed.

Visit-based assessments, extending beyond the sampling period, included timeline follow-back (TLFB) methods (39) to assess both number of cigarettes smoked each day over the preceding 7 days, and whether ENDS were used (yes/no) each day over the same period. CPD represents an average over this 7-day period.

Product evaluation. Product evaluation was based on the Modified Cigarette Evaluation Scale (40), asked in reference to both conventional and ENDS. The mCEQ is a 12-item scale, recently adapted for ENDS (41) with five factors: (i) enjoyment, (ii) craving reduction, (iii) satisfaction, (iv) reward, and (v) aversion.

Changes in smoking and cessation-related behaviors. Changes in smoking (CPD) are based on TLFB methods noted above. Cessation-related behaviors included the incidence of quit attempts (both any and those lasting ≥24 hours), floating abstinence (any 7-day period of self-reported nonsmoking, ever in study) and point prevalent abstinence (7-day nonsmoking at 4-month follow-up), the latter verified via carbon monoxide breathalyzer (<6 ppm). Motivation to quit (MTQ) in the next month was assessed through 0–10 VAS used previously (42).

Biomarkers of exposure. These included urinary cotinine, carbon monoxide, and NNAL. The latter was not included as a measure of toxicant exposure per se (as results would be specific to chosen product) but rather as a measure (like CO) to discriminate between conventional versus e-cigarette exposure. Urine cotinine

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Table 1. Sample characteristics ($n = 68$) at baseline, by study arm

	Control ($n = 22$)	16 mg ENDS ($n = 25$)	24 mg ENDS ($n = 21$)	*P*
Age, mean (SD)	42.3 (14.2)	43.3 (14.4)	40.9 (12.3)	0.8
Male (%)	36%	28%	57%	0.1
Race				0.6
White (%)	59%	56%	48%	
Black or African American (%)	41%	40%	52%	
Income				0.8
Less than $25k	55%	48%	48%	
More than $25k	36%	48%	48%	
Education				0.04
Some HS	5%	12%	5%	
HS	41%	8%	43%	
Some college	36%	56%	52%	
College or greater	18%	24%	0	
Employed full- or part-time (%)	68%	44%	52%	0.3
Age began smoking	15.8 (3.2)	18.4 (4.6)	19.0 (8.4)	0.2
Lives with another smoker (%)	27%	56%	33%	0.3
CPD	16.7 (11.3)	13.9 (4.9)	15.3 (8.3)	0.9
Heaviness of smoking (0–6)	3.1 (1.3)	2.6 (1.3)	2.9 (1.4)	0.6
Quit attempt in past year (%)	45%	36%	19%	0.2
Lifetime # quit attempts	4.0 (3.4)	5.5 (8.0)	3.0 (4.4)	0.2
Motivation to quit smoking in next month (0–10)	4.0 (3.9)	5.0 (3.8)	4.4 (3.1)	0.6
Confidence to quit smoking (0–10)	4.7 (3.0)	3.4 (3.0)	4.3 (3.1)	0.3
Ever used e-cigarette	9%	4%	33%	0.01
Anyone you know use an e-cigarette	55%	52%	57%	0.9
Intend to use e-cigarette in future (0–10)	5.4 (3.3)	5.6 (2.9)	5.5 (3.4)	0.9

was assessed via enzyme immunoassay (DRI Cotinine Assay, Thermo-Fisher Scientific), for which the limits of quantification were 34 ng/mL, and the inter-assay coefficient of variation for two controls were 3.6% and 3.0%. Urine total NNAL was measured in a separate laboratory (MLG) using UPLC-MS/MS as described previously (43), for which the limits of quantification were 5 pg/mL. Given skewed distribution of NNAL values, these data were first log-transformed before analyses.

Statistical analyses

Demographic and smoking history data at baseline were compared between the three groups via ANOVA models and χ^2 tests, as appropriate. Analyses of e-cigarette usage, including EMA data, were largely descriptive. Changes in biomarkers, CPD, and MTQ were all assessed via generalized estimating equations (GEE), testing group and time main effects and group × time interactions. These analyses were primarily focused on the entire 16-week study period. Whenever main or interaction effects were found, the outcomes were examined separately for both the sampling (first 4 visits) and the follow-up periods (weeks 8–16). Assessment of cessation-related behaviors (quit attempts, abstinence) followed an intent-to-treat approach, in which all missing cases were assumed as having no quit attempts/abstinence. These cessation-related behavior outcomes were compared between the three groups via χ^2 tests.

Results

Sample characteristics

Table 1 provides comparisons of selected demographic and smoking history data. There were few differences between groups at baseline. We did not include covariates in any following analyses due to the pilot scope of our purpose. Participants were primarily female, Caucasian (though with representative recruitment of African Americans), moderately dependent, and with moderate motivation to quit smoking.

Uptake and patterns of ENDS use

All but two ENDS participants attended at least one follow-up visit, and we restrict uptake data to these individuals alone (not assuming use/no use among those missing). Of these 44, all used the e-cigarette at least once (Fig. 2). Most participants reported a high frequency of use (based on TLFB), during the sampling period (>5 days per week), which decreased to about 3 days per week during follow-up. Over the 21-day sampling period, average duration of e-cigarette use was 15.4 days (SD=7.0) among 16 mg ENDS participants and 17.0 (SD=5.6) among 24 mg ENDS participants. Just under half (48%) of 24 mg ENDS participants used product all 21 days of the sampling period, versus 30% of 16 mg ENDS participants. Collapsing across both ENDS groups, the only predictors of increased duration of use were greater income ($P = 0.02$) and nicotine dependence ($P = 0.04$). Few control participants (<5%) used an e-cigarette during the sampling period, though 19% reported ENDS use during follow-up (Fig. 2;

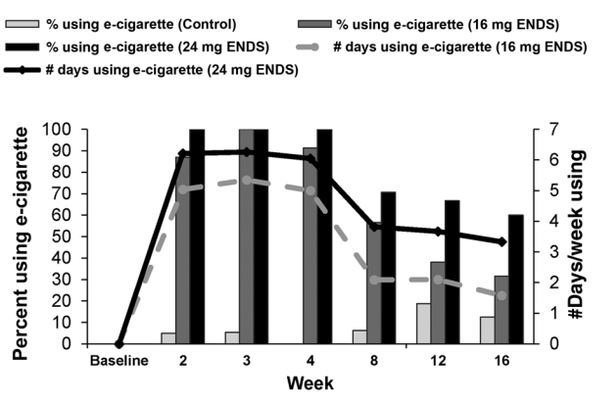

Figure 2.
Incidence and intensity of e-cigarette use during and beyond sampling period.

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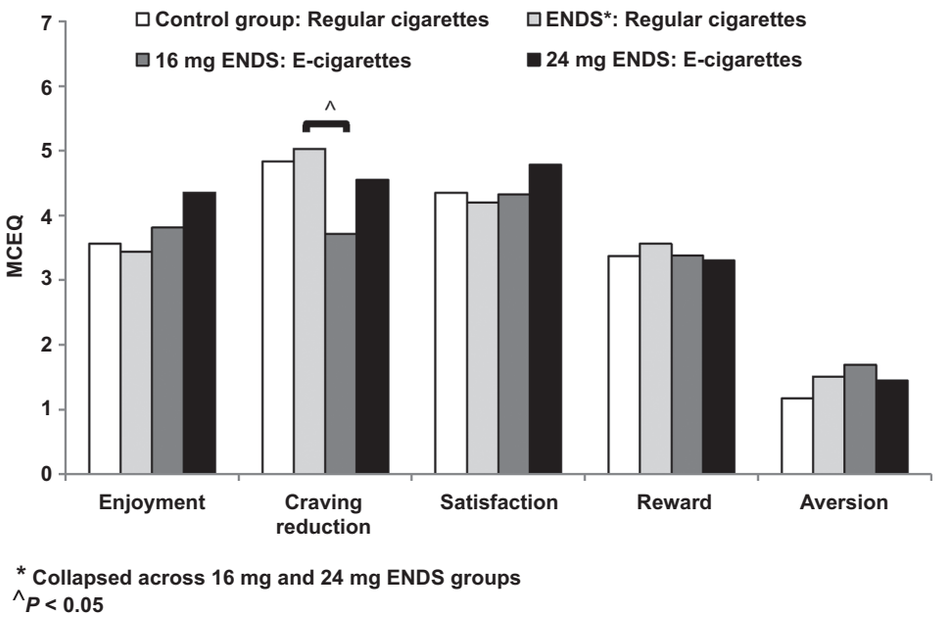

Figure 3.
Product evaluation of both cigarettes and ENDS at visit 4 after completion of ENDS sampling.

frequency of use not shown given $n = 4$). In the week preceding the final study visit (week 16); 60% (24 mg), 32% (16 mg), and 13% (Control) of participants were using e-cigarettes.

Participants who received the 24-mg product were significantly more likely to report independent purchase of an ENDS product compared with those who received 16 mg product and those in the control group (57% vs. 28% vs. 14%; $P < 0.05$). There were no differences in purchasing between 16 mg and Control participants. There was a significant time x group interaction for intention to use e-cigarette in future, overall ($P < 0.0001$), both within the sampling period ($P < 0.0001$) and throughout follow-up ($P = 0.02$), such that ENDS participants (both 24 mg and 16 mg) increased in intention during the sampling period (combined M=5.5; SD=3.1 at baseline vs. M=7.0; SD=3.1 at visit 4) whereas control participants decreased (M=5.4; SD=3.3 at baseline vs. M=2.7; SD=3.7 at visit 4); see Supplementary Fig. S1.

Beyond TLFB assessment at each laboratory visit, within-week EMA data provided a more detailed account of cigarette and e-cigarette use during the sampling period. Per-day cigarettes smoked (based on final EMA entry each day; not a complete day) dropped immediately upon onset of sampling period, and averaged 5.3 CPD (SD=1.1) for 24 mg ENDS, versus 8.4 CPD (SD=0.8) for 16 mg ENDS, versus 11.2 (SD=0.8) for control participants (See Supplementary Fig. S2). Number of puffing episodes per day was generally higher early in the sampling period among 24 mg ENDS participants (interaction $P < 0.05$; See Supplementary Fig. S3). Contextual correlates of smoking versus vaping, again based on EMA data and collapsed across all groups, show that use of both conventional and ENDS was most common when smoking was allowed (90% of cigarette smoking episodes and 83% of e-cigarette episodes) and when alone (73% of cigarette smoking episodes and 69% of e-cigarette episodes). When the participant was smoking a conventional cigarette with others present, these others were most likely also smoking conventional cigarettes (66% vs. 6% vaping vs. 28% not using anything). When others were present during e-cigarette episodes, these others were less commonly but still predominantly conventional smokers (59% vs. 29% vaping, vs. 12% not using anything). Over 40% of all cigarette episodes were indoors versus 58% outdoors, in contrast to e-cigarette episodes (65% indoor vs. 35% outdoor). Alcohol co-use was slightly higher during cigarette versus e-cigarette episodes (6% vs. 3%). The most common settings for cigarette smoking were home (60% of all episodes), car (18%) or another home (9%). The most common settings for vaping were home (51% of all episodes), public area (16%), or at work (12%).

Product evaluation

Product evaluation was asked for both conventional and ENDS. Three analyses were conducted, all based on the mCEQ and its adapted version for e-cigarettes: (i) control versus ENDS (collapsed across both 16 and 24 mg ENDS) for comparison of conventional cigarettes; (ii) conventional cigarettes versus e-cigarettes, within 16mg ENDS group; and (iii) same, within the 24 mg ENDS group. There were no differences in any of these measures at baseline, and thus no baseline adjustment was included when focused on outcomes at Visit 4, at the end of the sampling period. Results are shown in Fig. 3 for all five mCEQ subscales. Though not powered for tests of equivalence, products were generally rated similarly, for all three comparisons. The only exception was a significant difference within 16 mg ENDS participants, who rated their conventional cigarettes as offering higher craving relief than ENDS.

Changes in smoking and cessation-related behaviors

Consistent with EMA results, there was a significant time × group interaction for changes in cigarette smoking (CPD; averaged over the preceding 7 days before each laboratory visit), such that ENDS participants (both 16 and 24 mg) decreased their smoking, whereas control participants did not (Supplementary Fig. S4). These results also show that smoking decreases during the

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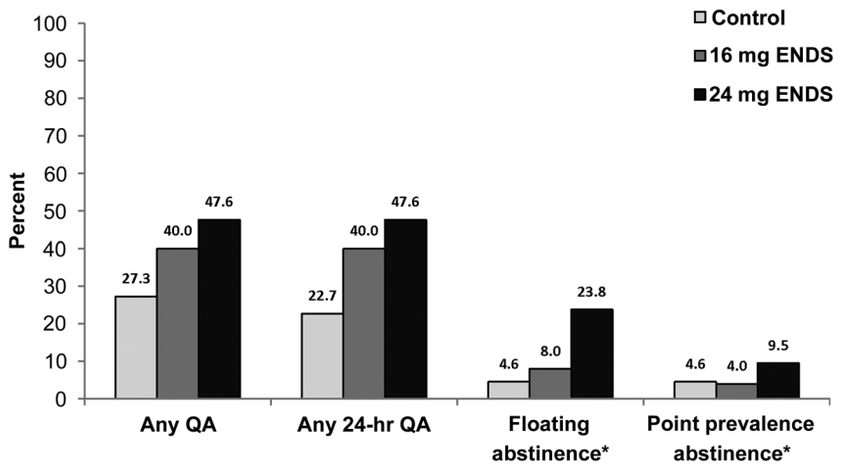

Figure 4.
Rates of quit attempts and cessation through 4 months. *7-day, no smoking, either floating (ever in study) or point prevalence at 4 months. Point prevalence abstinence at 4 month follow-up was CO verified; floating abstinence is self-report. Abbreviation: QA, quit attempt.

sampling period persisted across the follow-up period. Cigarette consumption decreased 45.1% for 24 mg ENDS participants during the sampling weeks, versus 30.2% reduction for 16mg ENDS participants, versus an increase of 0.7% for control participants. At the end of the sampling period, 35% (24 mg ENDS), 30% (16 mg ENDS), and 5% (control) of participants had reduced their smoking by at least 50% since baseline (overall $P = 0.07$). At the end of the entire study, respective rates of $\geq$50% reduction were 47% versus 16% versus 19% (overall $P = 0.09$). There was an overall significant interaction for motivation to quit ($P = 0.05$), such that ENDS participants (both 16 and 24 mg) increased in motivation to quit during the sampling period whereas control participants did not, though they did have comparable motivation to quit at end of study.

Cessation-related behaviors (quit attempts, floating and point prevalence abstinence) are depicted in Fig. 4. There were no statistically significant group comparisons across any of these outcomes, but there were clear trends for higher rates of all outcomes among 24 mg ENDS participants versus control participants, particularly for incidence rates for 24 hours quit attempts [48% vs. 23%; OR, 3.1; 95% confidence interval (CI), 0.8–11.5], and for floating abstinence (24% vs. 5%; OR, 6.7; 95% CI, 0.7–61.9).

Biomarkers of exposure

There were no group × time differences for urinary cotinine, carbon monoxide, or NNAL (Supplementary Fig. S5). Although these interactions were not statistically evident, some differences were compelling. There was a 25% reduction in expired CO within the 24 mg ENDS group by the end of the sampling period (vs. 10% in 16 mg ENDS and 3% in control). By the end of the study, reductions in CO were still evident: 29% versus 14% versus 12% decrease since baseline visit.

Adverse events

During the course of the study, eleven 24 mg ENDS participants (52%) reported a total of 21 adverse events, compared with nine 16 mg ENDS participants (36%) who reported 17 adverse events, and compared with 8 control participants (36%) who reported a total of 29 events. Collapsed across both ENDS groups, the most common side effects reported were cough (32%), nausea (24%), and mouth/throat irritation (16%), and in the control group, headache (24%), cough (21%), and mouth/throat irritation (17%). None of the adverse events resulted in study termination, or, among ENDS participants, early discontinuation of sampling.

Discussion

The current study presents a randomized yet naturalistic study of ENDS, with a focus on uptake and impact of ENDS over a 4-month period. An additional, unexpected strength of this study is the ability to compare (nonrandomized comparison) older versus newer e-cigarette devices, both first-generation devices but with exclusive differences on strength of nicotine delivery. Thus, our study affords a unique opportunity to examine two devices that vary only in nicotine strength (all other features constant) as compared with not sampling anything.

Uptake of ENDS was high, and higher among those who received newer/stronger product. All ENDS participants (both groups) used the e-cigarette given to them. Even after the conclusion of the 3-week sampling period, and through to the final study visit at 4 months, well over half of participants who were given a newer product were still using ENDS and vaping about half of each week. Although it is possible that participants held over product on hand from the sampling period, it is more telling that these same participants were significantly more likely to purchase their own product. Unfortunately, we are unable to determine whether they purchased the same, similar, or more advanced ENDS. This interest in further use of product is corroborated by their stated intentions on future use, which increased over time, versus control participants whose interest in ENDS waned. Participants generally rated cigarettes and ENDS similarly. These results are likely product-specific, but they stand in contrast to prior studies, similarly powered, showing favorability of cigarettes over e-cigarettes (44).

The contexts of smoking versus vaping were largely similar. Use episodes were generally bound to places or occasions where smoking was permitted and the individual was alone. In the presence of others, conventional smoking by that other person

was most common, both for cigarette smoking episodes and vaping episodes. The only contextual difference of note, not surprising, was that vaping was largely indoors whereas conventional smoking was largely outdoors. Future studies should also include assessment of nonuse contexts that would allow for comparisons to establish which situational factors determine use.

Changes in smoking behavior generally followed the same patterns as above with regard to uptake. ENDS sampling, regardless of older versus newer/stronger product, decreased cigarette smoking, whether measured via daily fluctuations during the sampling period or more robust measures (7-day weekly averages) over time and throughout the study. More than twice as many participants receiving 24 mg product (compared with control and 16 mg product recipients) reduced their smoking by 50% or more by the end of the trial. Across all cessation-related behaviors, outcomes were numerically but not statistically in favor of ENDS participants, particularly those receiving newer/stronger product. Although our study was solely based on a first-generation ciga-like device, these outcomes are consistent with a few laboratory-based studies showing superiority of second-generation (i.e., stronger) devices to control craving (45–47). These behavioral outcomes did not easily translate to changes in exposure. We had expected that CO and NNAL would roughly correspond to changes in smoking. This was partially supported in that there was a greater decrease in CO among participants who received the newer product. There were no changes in cotinine over time, nor between groups (or their interaction), consistent with the notion that smokers self-titrate their nicotine when using ENDS (48).

Our study provided ENDS free of charge, which we recognize is not truly naturalistic. Our intent was to remove cost and access barriers which would allow a more direct test of ENDS per se. Thus, we observed uptake and outcomes under conditions that were favorable to ENDS, and whether these same results would transfer to conditions when smokers have to pay for product is unclear. Forthcoming regulation of ENDS under the FDA will prohibit product sampling. Although this study does not provide sufficient data to overturn that ruling, our results are inconsistent with the interpretation that sampling does harm, at least to smokers (sampling directed to nonsmokers being a much greater public health concern).

Among our study limitations, the small sample size stands out as prominent. This was not a sufficiently powered trial, and most results were not statistically significant. Our intent was to highlight descriptive outcomes of uptake and general effect sizes for between group comparisons, all of which should guide a larger study. Second, we used a first-generation ciga-like product, which at the time of study development was the best option available, presumed to be a "starter" product among new converts. We have no reason to believe that outcomes would be worse for a second- or third-generation e-cigarette. In fact, there is reason to suggest that outcomes would be even stronger (vs. control conditions) for newer and more powerful ENDS devices, if only because they are generally more efficient in nicotine delivery, offer improved battery duration, and wider flavor assortment (45, 47), all of which presumably increase consumer appeal and eventual uptake. Third, our comparison group herein was a nonsampling control, as opposed to a placebo e-cigarette condition, studied elsewhere (49). We were less interested in the nicotine-specific effects of e-cigarette uptake and more interested on the aggregate experience of trying a new product versus not. Other, more active control groups might also be considered for future research, including: comparing ENDS sampling to provision of quit advice/materials, or perhaps samples of NRTs. Finally, EMA compliance was modest, somewhat dampening our rigor to assess daily fluctuations in use. Nonetheless, almost 2,500 EMA entries were recorded, mitigating this concern. The real challenges of EMA with respect to studies of ENDS pertain to quantification of use (e.g., operational definitions of puffs vs. puffing episodes), particularly when these metrics do not easily translate from conventional smoking (CPD). The current study provides some guidance worth consideration, as do others (50, 51), and newer devices with built-in technology to capture these metrics significantly expand the research potential.

Our study design is worth further comment, particularly given our prior research using similar methodology to examine sampling of other products. Randomized yet naturalistic designs allow for causal inferences on downstream behavior as well the more immediate effects of uptake and patterns of use. Prior trials have shown modest improvements in cessation-related outcomes when smokers sample NRT (34, 35, 52) but mixed or somewhat negative outcomes for snus (33). The relative response to multiple products can only come from studies that offer each, but these studies are rare (53, 54) and difficult if focused on long-term behavioral outcomes.

In sum, the results of this small pilot study suggest strong interest and uptake of ENDS among smokers, with favorable perception comparable with that of conventional cigarettes, and trends toward positive changes in cessation-related behavior. These findings, in need of replication within a larger trial, are generally consistent with reviews elsewhere that document positive effects of ENDS among adult smokers (2, 4, 55). More studies are needed to rigorously examine the naturalistic impact of ENDS on smoking behavior (56).

Disclosure of Potential Conflicts of Interest

M.L. Goniewicz is a consultant/advisory board member for Johnson & Johnson. K.M. Cummings reports receiving a commercial research grant from and is a consultant/advisory board member for Pfizer Inc., and has provided expert witness testimony for various plaintiffs in lawsuits involving cigarette manufacturers. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Development of methodology: M.J. Carpenter, B.W. Heckman, A.E. Wahlquist, T.L. Wagener, M.L. Goniewicz

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.J. Carpenter, M.L. Goniewicz

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.J. Carpenter, B.W. Heckman, A.E. Wahlquist, M.L. Goniewicz, K.M. Cummings

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.J. Carpenter, A.E. Wahlquist

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