Effect of unguided e-cigarette provision on uptake, use, and smoking cessation among adults who smoke in the USA: a naturalistic, randomised, controlled clinical trial

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eClinicalMedicine
2023;63: 102142

Published Online 15 August 2023
https://doi.org/10.1016/j.eclinm.2023.102142

Summary

Background As summarised in the most recent Cochrane review, the few clinical trials on e-cigarettes are largely focused on smoking cessation. We aimed to determine the naturalistic uptake, use, and impact of e-cigarettes among adults who may or may not want to stop smoking.

Methods In this naturalistic, randomised, controlled clinical trial, adult smokers, across the motivational spectrum and with minimal history of e-cigarette use, were recruited online from the general community within 11 cities across the USA. Participants were randomly assigned (2:1) to either receive either a free 4-week supply of flavoured, tank-style e-cigarette, or not. E-cigarette group participants received a battery and device with up to 30 pre-filled tanks, offered among five flavours, with minimal instructions on use. The study's primary purpose was to descriptively assess naturalistic uptake and usage of the e-cigarette, and to secondarily assess its impact on smoking behavior. The latter, assessed through six months of follow-up, included: a) self-reported 7-day point prevalence abstinence, b) incidence of quit attempts, and c) smoking reduction. This trial is registered at ClinicalTrials.gov, NCT03453385.

Findings Between 5/2018 and 3/2022, 638 adult smokers were enrolled and randomly assigned (427 in the e-cigarette group and 211 in the no-product control group). Uptake of e-cigarettes was robust: approximately 70% of participants used the product, with average usage exceeding 4 days per week during the initial 30 days. Based on an intent-to-treat approach where missing data is imputed as smoking, almost all behavioral outcomes favored the e-cigarette group relative to no-product control, including point prevalence abstinence at six months (Odds Ratio [OR] = 1.8; 95% Confidence Interval [CI] = 1.0–3.1), cumulative incidence of 24-hr quit attempts (OR = 1.5; 95% CI = 1.0–2.2), and having reduced smoking by at least 50% since baseline (OR = 1.8; 95% CI = 1.2–2.7). Results were similar under an alternative imputation.

Interpretation Complementing cessation-focused trials, results suggest that unguided e-cigarette use also leads to smoking cessation, allaying the notion that causal effects of e-cigarettes on cessation are not reflective of real-world scenario of self-determined use. For smokers who may not be able to quit using existing pharmacologic approaches, e-cigarettes may be considered to achive that purpose.

Funding National Cancer Institute.

Keywords: E-cigarettes; Smoking cessation; Randomised clinical trial; Public health

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Research in context

Evidence before this study

We searched PubMed for meta-analyses or reviews that summarized the evidence, from randomized clinical trials, on the effect of e-cigarettes on adult smoking cessation. Additional trials were identified through a separate search for "clinical trial" and "e-cigarette or electronic cigarette or vaping or ENDS." Findings from this search provide firm evidence to suggest that e-cigarettes have a causal role for smoking abstinence for adults who smoke. However, many of the trials within these reviews come from sources outside the U.S. and all of them use a design in which e-cigarettes are purposely used to achieve smoking cessation or reduction. That is, prior trials are based on structured, guided use of e-cigarettes, often among smokers wanting to quit, given support to do so. Some have expressed doubt as to whether the results from these structured and guided trials will translate into a real-world setting.

Added value of this study

Using a naturalistic but randomized design, the current study offers an opportunity to examine the uptake and causal impact of e-cigarettes in the absence of cessation-focused support. Randomized naturalistic studies are perhaps more reflective of real-world scenarios, where motivation to quit is not required and user decision guides use. As such, the current study also allows for subgroup analyses to assess these outcomes among smokers who may or may not want to quit smoking. Overall, findings from the current trial demonstrate robust uptake of e-cigarettes. As compared to those not receiving product, those who did showed greater movement towards abstinence from combustible smoking, across a range of outcomes. Many of these effects were evident among smokers across the motivational spectrum.

Implications of all the available evidence

Complementing cessation-focused trials, results suggest that unguided e-cigarette use also leads to smoking cessation., allaying the notion that causal effects of e-cigarettes on cessation are not reflective of real-world scenario of self-determined use.

Introduction

Systematic reviews[1,2] and meta-analyses[3–5] suggest a beneficial role for electronic (e-)cigarettes to promote smoking cessation. However, the individual trials that form the basis for this conclusion[6–13] are few in number and primarily come from outside the United States. Randomized trials are challenging to conduct within the U.S. given the regulatory environment that makes it difficult to assess (or claim) a therapeutic purpose for e-cigarettes, as would be the case for any study that is designed explicitly for this intent. In fact the vast majority of existing trials have involved adult smokers who expressed an interest in quitting and who were given instructions and support to do so (e.g., setting quit date, offering adjunctive cessation support). Some have suggested that the structured provision of e-cigarettes as a therapeutic intervention for smoking cessation, as demonstrated through these prior trials, does not translate to real world use; indeed a number of observational studies have not shown similar effects.[14] However, as non-randomized studies, observational cohort studies suffer from selection bias that often confounds interpretation.

Lacking in the literature are large-scale clinical trials that are both randomized (removing selection bias as to who does and does not use e-cigarettes) and naturalistic (allowing smokers to do as they wish). Randomized naturalistic studies are more inclusive of a broad range of smokers, including those who may not want to quit. They also provide minimal instruction and/or requirement to use e-cigarettes. Such trials are perhaps more reflective of real-world scenarios, where motivation to quit is not required and user decision guides use. As such, randomized naturalistic studies allow for analyses of self-determined product uptake/use *and* causal effects on smoking cessation, if any. In combination with cessation-focused RCTs above, such trials have the potential to provide guidance to inform regulatory policies regarding e-cigarettes.

To date, only one such randomized, naturalistic trial exists.[15] Our group conducted an initial pilot trial of early-generation e-cigarettes, focusing on product uptake and effects on cessation. Results from the trial suggested that cigarette smokers are willing to use e-cigarettes, with numerically if not statistically significant trends toward reduced cigarette smoking and positive changes in cessation-related behaviors.

The current study is the first large-scale trial to assess the uptake and impact of e-cigarettes when provided beyond a treatment context and without explicit instructions to switch. To our knowledge, it is the largest e-cigarette trial yet conducted within the US.

Methods

Study design

The trial recruited adult smokers in 11 cities across the US and randomized them to receive a free 4- week supply of e-cigarettes (n = 427) or not (n = 211). No additional product was offered beyond one month, though e-cigarette use was measured throughout follow-up, which occurred via phone surveys occurred at Weeks 1, 2, 3, 4, 8, 12 and 24. E-cigarette devices and tanks were purchased directly from NJoy with grant

funds. All study procedures were approved by the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) and was registered at ClinicalTrials.gov (NCT03453385). Findings below are presented in concordance with CONSORT reporting guidelines.

Participants

Eligibility criteria included: a) age 21+ (abiding by tobacco sales requirements), b) current smoker of ≥5 cigarettes per day for ≥1 year, c) no known recent history of cardiovascular distress, d) neither pregnant nor breastfeeding, and e) no current use of smoking cessation medication. Inclusion was further restricted to participants with minimal history of e-cigarette use, defined as not having purchased e-cigarettes in the prior six months, nor having ever used a tank system weekly, nor having used any e-cigarette of any kind in the preceding six months. Participants were recruited through online methods (e.g., Craigslist), which provided a direct link to an secure online platform (e.g., REDCap) for initial screening. Upon initial eligibility, individuals provided their contact information and were subsequently consented through one of two channels, available upon preference. The first option allowed for mailed consents (postage-paid return reply); the second was via synchronous teleconsent; both provided opportunity to discuss study details and ask any questions with study staff prior to consent. Upon receipt of the mailed consent packet or completion of teleconsent, participants were scheduled for a baseline (Week 0) intake call, during which they were randomized to assigned group. As a remote trial, the unique details of screening and consent are provided elsewhere.[16]

Among the 11 cities selected for participant recruitment, the local Charleston SC metro area was included, with the intent to recruit a sub-sample of participants (n = 120) who could come into the research lab to provide biochemical verification of smoking behavior. However, the COVID-19 pandemic significantly compromised these plans. University shut-downs and delayed re-opening disallowed many in-person study visits, and collection of biomarkers was not feasible as intended. Thus, while the trial included a local subsample, there was insufficient data to report on biomarker outcomes (57 biospecimen samples at Week 4, and 39 at Week 24, across both groups).

Randomization

Randomization occurred via stratified, mixed block design, stratifying on local vs. national enrollment and on desire to quit smoking: 0–6 vs. 7–10 on a VAS scale. Randomization was 2:1 (e-cigarette:control) to increase the precision of parameter estimates around e-cigarette product uptake. The randomization allocation was created by the study statistician and uploaded into REDCap so that the research staff team was blinded to the sequence and could randomize individuals as they were eligible for participation. Randomization did not include any masking.

Procedures

The general aim within the e-cigarette group was to approximate the real-world scenario in which smokers are exposed to e-cigarette products and self-decide if and how to use them. The guiding intent was to use the most efficient, non-modifiable product on the market at the time of study initiation, with the goal of optimizing user satisfaction and avoiding the possibility of tank adulteration [spilling, adding more]. NJoy's pre-filled tank and battery was selected for this purpose, coinciding with the FDA decision to use it as a prototype for a Standardized Research E-Cigarette (SREC) for research purposes. The NJoy device was a closed tank system, sufficiently powered (1000 mAh) with 3 ml prefilled nicotine (15 mg/ml). Participants could choose up to 2 flavors among 5 offered: tobacco, menthol, blue/blackberry (one flavor), apple melon, or iced fruit, and could change selection at 2nd shipment.

The product was provided in two ~2-week shipments: 30 tanks total, under the rationale that one month would allow for an adequate acclimation period in which participants could determine if and how they would use it. In rare instances where shipments were not received (n = 14; 3%), additional product was sent in deviation from the protocol. Adjunctive messaging, provided via phone at baseline call and within mailing of product, gave cursory background and suggestions on how it could be used but emphasized that choice on if or how to use e-cigarettes was completely up to the participant. Full messaging is provided within Supplemental Materials, but specific excerpts include:

We will provide an e-cigarette device for you to use over the next four weeks. We'll send you everything you need via mail, and you'll receive it in a few days. ... The most important thing to tell you now is that you can use these e-cigarettes however you like, as much or as little as you like. You can reduce your smoking, quit smoking entirely, or just use e-cigarettes in places where you cannot smoke ... You are not required to use the e-cigarettes, but you might want to give them a try.

Participants were also told that e-cigarettes were 'likely safer' than combustible cigarettes (the most conservative, IRB-approved messaging at the time of study onset), and, in response to e-cigarette or vaping use-associated lung injury (EVALI) which arose as a concern midway through the study, brief caution was expressed. While provision of free product is not naturalistic, the trial's design allowed for the assessment of naturalistic outcomes of product use when cost is not a barrier.

Participants in the no-product control group did not receive any product but were compensated nominally more for study participation than the e-cigarette group ($320 vs. $240) to offset concerns about attrition. Note that a placebo comparison is specifically not warranted in a naturalistic product use design. A study of e-cigarette provision, inclusive of any expectancy effects, is properly controlled via no provision of product.

Outcomes

The study's primary purpose was to assess naturalistic uptake and usage of the e-cigarette. Thus, descriptive information is provided in regard to: a) any use and b) number of days of use and c) puffing episodes on days of use, each assessed weekly for the first month and then episodically thereafter. Puffing episodes were guided by precedent from other studies,[17] and explained to participants as "the number of times per day that you use the e-cigarette (one time consists of about 15 puffs or 10 min of use)." While these uptake outcomes pertain primarily to the e-cigarette group, control participants could also use e-cigarettes, on their own accord, and thus, these outcomes are reported as well.

While not a cessation-driven trial, the study was powered on these outcomes under the rationale that: a) cessation might naturally occur, b) it would be missed opportunity to be under-powered to detect any between-group differences, and c) readers would be interested in these study outcomes in comparison to other trials. Thus, while cessation was not the primary objective, it did serve as the outcome on which the study was powered (see below). Additional measures of cessation included: a) 7-day abstinence at each weekly visit, b) 'floating abstinence;' i.e., having ever achieved 7-days of non-smoking, throughout follow-up,[18] and c) incidence of 24-hr quit attempts. Other related outcomes include changes in cigarette smoking and smoking reduction, changes in motivation and confidence to quit smoking (MTQ, CTQ, both assessed via 0–10 scales where 0 = none and 10 = maximum confidence/motivation), product dependence, and product co-use. Cigarette and e-cigarette dependence is based on the Penn State Nicotine Dependence Index,[19] with separate but similar wording for each, allowing for comparison across products (range 0–20 for each). Consistent with national recommendations for trial outcomes[18] and early trials of e-cigarettes,[6,7,20] smoking reduction is operationalized as achieving a ≥50% reduction in cigarettes per day (CPD) since baseline (% yes), thought to signify a meaningful reduction in toxicant exposure; i.e., harm.

Sample size determination

Per above, sample size estimations were based on cigarette cessation: 7-day point prevalence abstinence at 6-month follow-up. Base rates came from prior nationwide trials of similar design conducted by our group, in which 6-month abstinence rates within the control group ranged 4–13%.[21,22] Other estimates suggest ~5% for population-based quitting.[23] Ultimately, a base rate of 8% was chosen. Anticipated quit rates in the e-cigarette group were derived from the most relevant study published at the time of study design: an uncontrolled observational cohort (i.e., naturalistic) study of smokers given e-cigarettes for up to 6 months,[24] in which 23% (intent-to-treat; ITT) and 33–39% (respondent only analyses) were quit at 6 months. Since the current trial provided e-cigarettes for 1 month only, a lower quit rate was anticipated. The trial was thus powered to detect a difference in rates of abstinence of 8% vs. 16% (RR = 2.0), requiring 600 participants (400 e-cigarette vs. 200 control). Inflating by 10% to account for potential attrition, the final anticipated sample size was estimated at 660 participants. The final actual sample size was 638 (97% of target); unavailability of product supply in the final months of recruitment precluded additional enrollment.

Statistical analysis

Measures of uptake are largely descriptive, focusing primarily on the e-cigarette group. Binary cessation outcomes were analyzed two ways: (1) coding missing data as returned to smoking (labeled as Missing = Smoking; M = S) as per suggested practice[25] and (2) utilizing generalized linear mixed models (GLMMs) with binary distribution, logit links, and random residual options to allow time points with missing data to be informed by prior collected data. No imputations were made for continuous outcomes. For M = S analyses, logistic regression models were used for each of the cessation outcomes noted above, with the main effect of intervention group included. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined from the models for (1) point prevalence abstinence at weekly follow-up, (2) floating abstinence, (3) cumulative incidence of 24 hr QA's and (4) achieving 50% reduction in CPD. The GLMMs were created similarly with main effects for intervention group, time, and an interaction between time and group. Estimate statements from the models were used to determine group differences at each time point of interest and reported as ORs and 95% CIs. Note that both M = S and GLMM outcomes are shown in Table 2, but the text within Results reports M = S outcomes (outcome percents, ORs, 95% CIs) only. Per the original protocol (Supplemental Materials), covariates were not included in models unless baseline differences suggested need for otherwise.

General linear models (GLMs) were used to measure the relationships between group and time for continuous outcomes of interest such as CPD, MTQ, CTQ, and dependence. Interactions between time and group were initially included in models and were removed if not significant at an $\alpha = .1$ level of significance, leaving the main effects of time and group.

Patterns of use and dual use over time are also largely descriptive, and in cases of missing data, the last observation was carried forward.

As noted above, the current trial stands in contrast with many existing RCTs, in that study recruitment was open to smokers across the motivational spectrum, without requirement to quit. Accordingly, many of the above outcomes were separately assessed among smokers high (7–10 on 10-pt scale) and low in motivation to quit (0–6), to determine if the effects were restricted to merely the former. Notably, the trial was not powered on these post-hoc sub-group differences; the intent herein is to compare effect sizes only.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors MJC, AEW, and TTS had full access to the data throughout the study. All authors contributed to methods and manuscript editing. MJC had final responsibility for decisions on publication.

Results

Recruitment flow, initiated 5/2018 and ending 3/2022, is shown in Fig. 1, and sample characteristics are shown in Table 1. For all follow-up timepoints, retention favored the no-product control group ($P < .05$ for each). The sample had broad demographic diversity: 31% non-White, 14% Hispanic or Latino, and heterogeneity across educational, employment, and income strata. By design, individuals were represented across the motivational spectrum of wanting to quit. There were no group differences at baseline. Thus, as per protocol, no covariates were included in subsequent analyses.

E-cigarette uptake

Fig. 2 shows the percentage of participants reporting use of an e-cigarette and frequency of use in each group. In the e-cigarette group, product use ranged from 60 to 70% during the 4-week sampling period and decreased over time (vs. 9–13% within no-product group during this same period). At 6-months, 44% of the e-cigarette sample group still reported use of an e-cigarette vs. 16% in the no-product control group. On average, frequency of use within the entire e-cigarette group (inclusive of non-users) ranged from 2.0 to 4.5 days per week during the initial four weeks, decreasing to two days per week at final follow-up. Among users only, frequency of use was more regular: 4–6 days per week throughout the entire course of the study. Frequency of e-cigarette use was much lower in the no-product control group. However, among users only, the daily usage levels were comparable to those in the e-cigarette group (Fig. 2). The same was true for amount of use within a day; i.e., puffing episodes (Supplemental Materials). Thus, participants in the e-cigarette group had a much higher uptake of the product overall (as expected), but among users, frequency and amount of use were similar, i.e., free product promoted increased access/use but did not increase frequency or amount of use. Another measure of uptake is product adoption; i.e., independent purchase of e-cigarettes at any time throughout the follow-up period. On this metric, there were no group differences on purchase of either another device or additional nicotine liquid (19% within e-cigarette group vs. 20% within no-product control group).

Between group comparisons on all measures of uptake were similar within each group of smokers who were highly motivated to quit vs. those who were not.

Smoking cessation, quit attempts, smoking reduction

As shown in Table 2, participants within the e-cigarette group were more likely to self-report cigarette abstinence after the 4-week trial period and at all follow-up assessments through six months. At final follow-up, 14% vs. 8% (M = S) of participants reported abstinence from cigarettes (OR = 1.79; 95% CI: 1.02–3.16). The cumulative incidence of quit attempts also favored the e-cigarette group throughout follow-up (26% vs. 19% at Week 24). Differences in floating abstinence, i.e., having ever achieved 7 days of non-smoking, were non-significant (e-cigarette: 17% vs. no-product control: 12%). GLM analyses revealed a significant group by time effect for changes in cigarette smoking ($P < .0001$), with a greater reduction in the e-cigarette group over time. A larger percentage of participants in the e-cigarette group achieved at least 50% reduction in CPD throughout follow-up compared to the no-product control group (Table 2; 28% vs. 18% at Week 24). Additional post-hoc analyses that further examined a) frequency of e-cigarette use and b) e-cigarette users vs. non-users, are presented in Supplemental Materials. At both Week 12 and Week 24, e-cigarette users in the e-cigarette group (at Week 4) had significantly higher rates of cessation-related behavior (quit attempts, point prevalence abstinenence, 50% reduction in CPD) as compared to Week 4 non-e-cigarette users in the no-product control group (Supplemental Table S5).

Post-hoc subgroup analyses (also in Table 2) demonstrated roughly comparable effects for each of the outcomes above among participants with low and high motivation to quit, as reported at baseline. While absolute rates of outcomes were lower among the low-motivated participants, the effect size (odds ratio) was comparable overall between low vs. high motivation. Thus, cessation effects were not restricted to smokers wanting to quit.

Motivation and confidence to quit smoking

GLM analyses revealed a significant group by time effect for both motivation ($P < .0001$) and confidence to quit

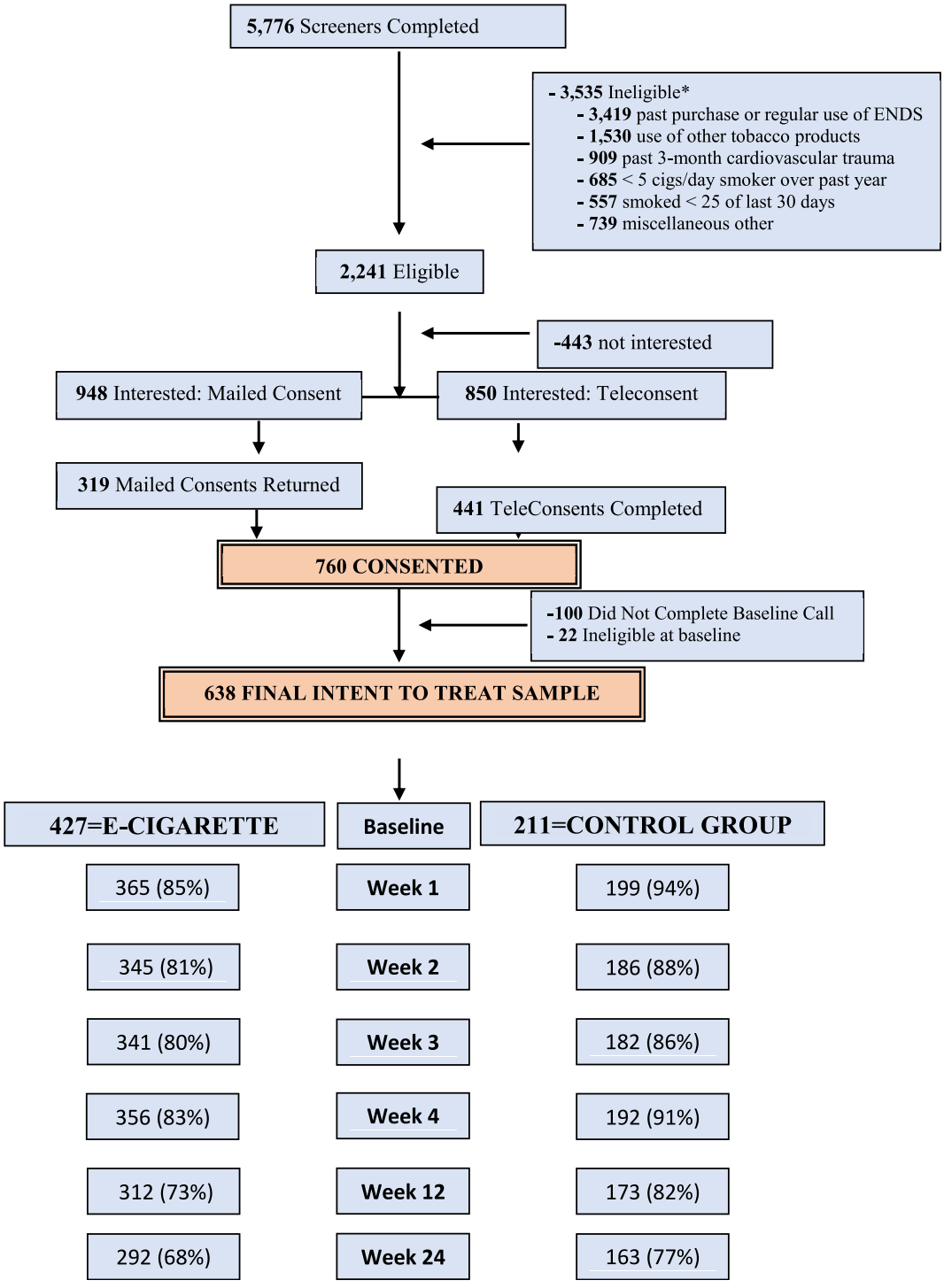

Fig. 1: **Consort flow of recruitment.** Legend: * reasons not mutually exclusive; five most common reasons shown (others available upon request).

	Control N = 211	E-Cigarette N = 427
Demographics		
Age, mean (SD)	42.0 (11.9)	42.4 (11.2)
Gender, No. (%)		
Male	91 (43.1)	205 (48.0)
Female	120 (56.9)	222 (52.0)
Race, No. (%)		
White	146 (69.2)	291 (68.2)
Black	32 (15.2)	86 (20.1)
Other	33 (15.6)	50 (11.7)
Hispanic or Latino, No. (%)	27 (12.8)	63 (14.8)
Education, No. (%)		
High School or less	76 (36.0)	121 (28.3)
Some College	99 (46.9)	216 (50.6)
College Graduate or more	36 (17.1)	90 (21.1)
Employment Status, No. (%)		
Unemployed	54 (25.7)	105 (24.7)
Employed Full/Part Time	127 (60.5)	236 (55.4)
Other	29 (13.8)	85 (20.0)
Household Income, No. (%)		
<$25 k	62 (31.0)	135 (33.0)
$25–50 k	80 (40.0)	138 (33.7)
$50–75 k	34 (17.0)	73 (17.9)
>$75 k	24 (12.0)	63 (15.4)
Ever Diagnosed Mental Health Disorder[a], No. (%)	42 (19.9)	85 (19.8)
Smoking History		
Cigarettes per Day, mean (SD)	14.8 (7.2)	14.8 (7.2)
Cigarette Dependence (0–20), mean (SD)		
Motivation to Quit Smoking (0–10), mean (SD)	4.5 (3.1)	4.3 (3.3)
Quit Attempt in Past Year, No. (%)	58 (27.5)	96 (22.5)
Ever Use of E-Cigarette, No. (%)	77 (36.5)	181 (42.4)
Smoker in Household, No. (%)	87 (41.2)	162 (37.9)
E-Cigarette User in Household, No. (%)	11 (5.2)	17 (4.0)

Note: No between group differences on any baseline variable. [a]Asked specifically to include: depression, anxiety, bipolar, ADHD, and/or schizophrenia disorders.

Table 1: **Baseline characteristics of participants (N = 638).**

smoking ($P < .0001$), with significant increases in each within the e-cigarette group, but not the no-product control group. The same was true among subgroups of low and high motivation to quit, except for CTQ among highly motivated smokers (time by group interaction not statistically significant).

Cigarette/E-cigarette dependence

Using the Penn State Nicotine Dependence Index (possible range 0–20), GLM analyses revealed a significant group by time effect for cigarette dependence ($P < .0001$), with significant decreases over time within e-cigarette sampling group but not no-product control group (Fig. 3). The same was true within sub-groups of smokers motivated to quit and not. Within the e-cigarette group alone, the same instrument allows for comparison of dependence across products (also Fig. 3). E-cigarette dependence increased slightly through Week 4 and then declined. At all timepoints, e-cigarette dependence was significantly lower than combustible cigarette dependence.

Concurrent/dual use

By Week 4, 68 (16%) of smokers within the e-cigarette group were exclusive smokers, 43 (10%) were exclusive e-cigarette users, 315 (74%) were co-using, and 1 (1%) was completely abstinent from both products. Among Week 4 mono-smokers (n = 68), 2 (2.9%) achieved complete abstinence (of both products) at Week 24, 5 (7.4%) had become dual users; 1 person (1.5%) became an exclusive e-cigarette user, but the majority (n = 60; 88.2%) maintained mono-smoking. Among exclusive e-cigarette users at Week 4 (n = 43), 13 (30.2%) achieved complete abstinence at Week 24, 2 (4.7%) returned to smoking and were dual using, 19 (44.2%) were still exclusive users of e-cigarettes, and 9 (20.9%) relapsed to

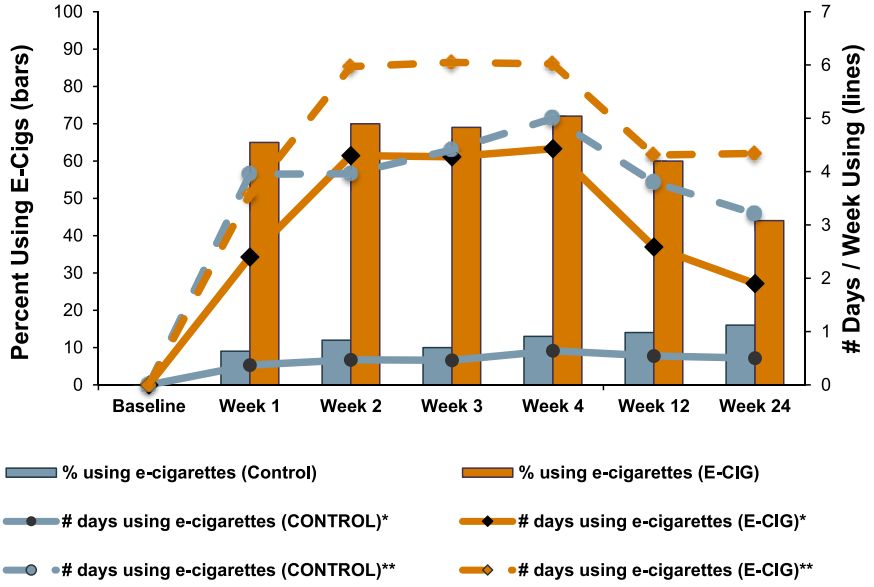

Fig. 2: **E-Cigarette uptake.** Legend: * non-users included (0 days). ** Users only. Solid blue bars represent percent using e-cigarette within no-product control group. Solid orange bars represent percent using e-cigarette within e-cigarette group. Solid blue lines represent number of days using e-cigarette, with non-users included, within the no-product control group. Solid orange lines represent number of days using e-cigarette, with non-users included, within the e-cigarette group. Dashed blue lines represent number of days using e-cigarette, based on users only, within the no-product control group. Dashed orange lines represent number of days using e-cigarette, based on users only, within the e-cigarette group.

exclusive smoking. Among dual users at Week 4 (n = 315), 18 (5.7%) achieved complete abstinence at Week 24, 187 (59.4%) were still dual using, 91 (28.9%) were relapsed to mono-smoking, and 19 (6.0%) became exclusive e-cigarette users. Full trajectories of use, across both groups, are provided within Supplemental Materials, as are rates and levels of smoking reduction among dual users.

Adverse events

Within the e-cigarette group, 180 people (42%) reported a total of 360 adverse events (AEs), of which 7 (2%) were severe, 113 (31%) were moderate, and 232 (64%) were mild (8 additional uncoded). The most common adverse events were cough (17%), headaches (12%), and increased phlegm (12%). There was one serious adverse event that was questionably associated with e-cigarette use: a participant-reported case of asthma-induced hospitalization, with "liquid in the lung", possibly attributed to increased nebulizer use and/or e-cigarette use. Within the no-product control group, 86 people (41%) reported a total of 197 AEs, of which 7 (4%) were severe, 60 (30%) were moderate, and 124 (63%) were mild (6 additional uncoded). The most commonly reported AEs in the control group were cough (20%), increased phlegm (18%), and headaches (8.1%). The average (SD) number of AEs reported per person in the e-cigarette group was 0.9 (1.5), ranging from 0 to 7 AEs per person, as compared to the no-product control group with an average of 0.8 (1.3) AEs per person, ranging from 0 to 9.

Discussion

While debate on the role of e-cigarettes for tobacco control remains polarized, many of the concerns against them have been distorted.[26] Randomized clinical trials offer the strongest evidence as to whether they can help smokers achieve abstinence from combustible products. To our knowledge, this is the first naturalistic clinical trial of e-cigarettes in the US, reflecting the real-world scenario whereby a wide range of adults who smoke self-decide if, how, and for what purpose to use e-cigarettes.

Study results complement and are largely consistent with the handful of clinical trials assessing causal effects of e-cigarettes on smoking cessation.[6–12] Study results are also consistent with a handful of population-based studies that have shown an association between e-cigarete use and smoking cessation,[27–29] as well a number of studies that have shown that frequency of use is an important determinant in this association.[30–32] As a naturalistic randomized trial, the current study was aimed primarily to examine the uptake of and outcomes from e-cigarettes, across a broad range of smokers given minimal guidance or instructions on use. Uptake was strong, with 70% of participants using the e-cigarette, with moderate frequency. As a whole and with few exceptions, cessation and smoking reduction outcomes favored the e-cigarette

	Overall				High Motivation to Quit				Low Motivation to Quit			
	Control (n = 211)	E-Cigarette (n = 427)	OR[a,f] (95% CI)	OR[a,g] (95% CI)	Control (n = 58)	E-Cigarette (n = 116)	OR[a,f] (95% CI)	OR[a,g] (95% CI)	Control (n = 153)	E-Cigarette (n = 311)	OR[a,f] (95% CI)	OR[a,g] (95% CI)
Point Prevalence Abstinence												
Week 4	2 (1%)	44 (10%)	12.00 (2.88–50.02)	13.40 (3.35, 53.54)	1 (2%)	20 (17%)	11.88 (1.55–90.87)	12.68 (1.84, 87.44)	1 (1%)	24 (8%)	12.71 (1.70–94.87)	14.40 (2.18, 95.28)
Week 12	8 (4%)	61 (14%)	4.23 (1.98–9.01)	4.99 (2.38, 10.46)	4 (7%)	25 (22%)	3.71 (1.22–11.23)	3.92 (1.35, 11.36)	4 (3%)	36 (12%)	4.88 (1.70–13.96)	5.98 (2.22, 16.16)
Week 24	17 (8%)	58 (14%)	1.79 (1.02–3.16)	2.12 (1.21, 3.72)	10 (17%)	24 (21%)	1.25 (0.55–2.83)	1.34 (0.60, 3.01)	7 (5%)	34 (11%)	2.56 (1.11–5.92)	3.12 (1.41, 6.91)
Floating Abstinence[c]												
	26 (12%)	72 (17%)	1.44 (0.89–2.34)	0.82 (0.38, 1.74)	10 (17%)	34 (29%)	1.99 (0.90–4.39)	0.44 (0.13, 1.52)	16 (11%)	38 (12%)	1.19 (0.64–2.21)	1.13 (0.44, 2.88)
24 hr Quit Attempt[d]												
Through Week 4	14 (7%)	65 (15%)	2.55 (1.39–4.66)	2.69 (1.47, 4.93)	8 (14%)	36 (31%)	2.81 (1.21–6.54)	3.17 (1.35, 7.44)	6 (4%)	29 (9%)	2.52 (1.02–6.21)	2.64 (1.07, 6.52)
Through Week 12	20 (9%)	89 (21%)	2.51 (1.50–4.21)	2.68 (1.60, 4.50)	8 (14%)	45 (39%)	3.96 (1.72–9.13)	4.40 (1.89, 10.23)	12 (8%)	44 (14%)	1.94 (0.99–3.78)	2.04 (1.04, 4.00)
Through Week 24	40 (19%)	110 (26%)	1.48 (0.99–2.23)	1.57 (1.04, 2.36)	16 (28%)	51 (44%)	2.06 (1.04–4.08)	2.23 (1.12, 4.46)	24 (16%)	59 (9%)	1.26 (0.75–2.12)	1.32 (0.78, 2.23)
≥50% CPD[e] Reduction												
Week 4	19 (9%)	140 (33%)	4.93 (2.95–8.23)	5.90 (3.51, 9.93)	8 (14%)	57 (49%)	6.04 (2.63–13.85)	7.13 (3.03, 16.75)	11 (7%)	83 (27%)	4.70 (2.42–9.12)	5.65 (2.89, 11.06)
Week 12	26 (12%)	126 (30%)	2.98 (1.88–4.72)	3.81 (2.37, 6.13)	12 (21%)	44 (38%)	2.34 (1.12–4.90)	2.60 (1.19, 5.68)	14 (9%)	82 (26%)	3.56 (1.94–6.51)	4.76 (2.56, 8.86)
Week 24	38 (18%)	119 (28%)	1.76 (1.17–2.65)	2.25 (1.46, 3.47)	15 (26%)	44 (38%)	1.75 (0.87–3.52)	2.11 (0.98, 4.54)	23 (15%)	75 (24%)	1.80 (1.07–3.00)	2.34 (1.37, 4.01)

Notes: %s reported are based on the full-group denominator where missing = smoking (M = S). [a]OR (95% CI) = Odds Ratio and corresponding 95% Confidence Interval. [b]High (7–10 on Visual Analog Scale) vs. Low (0–6) Motivation to Quit Smoking. [c]Any 7-day period of non-smoking, ever throughout study follow-up (Weeks 0–24). [d]Cumulative incidence of any 24-h quit attempt through week 4, 12, 24. [e]CPD: Cigarettes per day. [f]Estimates from models were imputed where missing = smoking (M = S). [g]Estimates from generalized linear mixed models.

Table 2: **Cessation-related behaviors: overall and among sub-groups of high vs. low motivation to quit smoking.[b]**

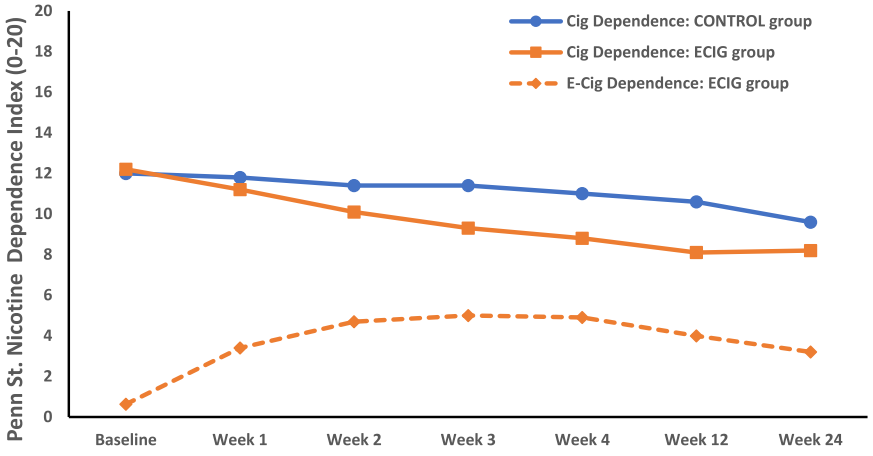

***Fig. 3:* Cigarette and E-Cigarette dependence.** Legend: [a] E-cigarette dependence within control group not shown given low uptake. Solid blue lines represent cigarette dependence scores within no-product control group. Solid orange lines represent cigarette dependence scores within e-cigarette group. Dashed orange lines represent e-cigarette dependence scores within e-cigarette group.

group, even among smokers who expressed little interest in quitting at study outset. Smokers in the e-cigarette group showed declines in cigarette dependence and increased motivation and confidence to quit smoking, with minimal reported adverse events compared to the no-product control group.

Not unlike other e-cigarette trials, dual use was the modal outcome among smokers in the e-cigarette sampling group, both at short term (Week 4) and final follow-up (six months). It is important, however, to put this in the context of smoking reduction.[26] Sustained dual users demonstrated substantial reductions in combustible cigarette smoking. Furthermore, there was a greater proportion of smokers achieving cigarette abstinence among early dual users in the e-cigarette group than in the entirety of the control group. Thus, while the provision of e-cigarettes did prompt dual use, even that led to smoking cessation.

The regulatory climate for e-cigarettes within the United States is far different from that in other countries such as England, where the Royal College of Physicians has given clinical support for e-cigarettes, not only as a harm reduction alternative to combustible smoking, but as a definitive strategy to abstain from it.[33] Free starter kits, largely congruent with the guiding philosophy of the current trial, will be liberally distributed to one million smokers in England in a forthcoming campaign to drastically reduce smoking rates (goal of <5% by 2030).[34] Distribution of starter kits naturally give way to questions of cost-effectiveness, particularly among smokers who are not yet planning to quit. The current trial was not focused on cost-effectiveness outcomes, but a separate analysis of a prior trial of nicotine replacement therapy (NRT) sampling, using similar methods as those herein, demonstrated actual cost-savings.[35] Whether the same is true for e-cigarettes is unclear, but one might speculate that roughly comparable cost between NRT and e-cigarettes and superior outcomes (e-cigarettes > NRT), the same might hold.

In contrast to above, many public health organizations in the U.S. actively focus almost exclusively on potential risks, even if such risks are inflated.[36] The current trial was not intended to change US regulatory policy on e-cigarettes, but it certainly has bearing on it. While the current trial is not an exact real-world scenario (no randomized trial can be), it closely approximates it. A true real-world scenario, as purported through observational studies, is confounded by selection bias. The current study overcomes selection bias while keeping the design naturalistic. As such, the results directly address the concern that any causal link between e-cigarettes and smoking cessation is restricted to interventional studies only.

Regulatory agencies continue to weigh the risks of e-cigarettes for adolescents and non-smokers with the potential for these products to benefit adults who smoke. The results of the current study provide additional evidence that e-cigarettes have the potential to benefit public health for current smokers who try e-cigarettes by reducing smoking and promoting cessation.

Strengths of the study include its large sample size with diverse representation. Randomization removes selection bias that is often found in cohort studies of e-cigarette use. Nonetheless, the lack of biochemical verification of smoking cessation or reduction stands as the most prominent study limitation. Even among the locally recruited sample, COVID-related closures and work-from-home requirements severely compromised compliance with biomarker collection (urine and carbon monoxide) procedures. With the advance of remote CO collection,[37,38] these methods were added late into the study but were still insufficient in returned samples

(among a subset of locally recruited participants) to adequately analyze. As a secondary limitation, study retention was lower than anticipated, and this too may be a consequence of pandemic-related closures. Finally, given higher attrition within the e-cigarette group relative to the no-product control group, between group differences may be under-estimated, especially when imputing missing = smoking or no e-cigarette use.

Growing evidence suggests that e-cigarettes can be a catalyst for smoking cessation. Current findings indicate that this may be true even within unstructured and unguided use. This evidence must be balanced with the equally important public health need to minimize adolescent uptake of any form of nicotine, combustible and other.

Contributors

MJC was responsible for study conceptualization, funding acquisition, investigation, methodology, project administration, supervision, and writing, both original and editing.

AEW was responsible for formal analysis, methodology, and writing, both original and editing. MJC, AEW, and TTS had access to and verified all data presented herein. JD, KMG, KMC, GW, TLW and MLG assisted with methodology and manuscript editing. TTS assisted with study methodology, project administration, and manuscript editing.

Data sharing statement

Deidentified data will be available upon request, beginning upon publication and ending 5 years thereafter, in accordance with legl frameworks and upon protocol approval from Institutional Review Board (IRB). Requests should be sent to MJC via email, and will be reviewed on a case-by-case basis. Investigator support will also be reviewed on a case-by-case basis.

Declaration of interests

KMC has served as a paid expert witness in litigation filed against the tobacco industry. KMG has provided consultation to Jazz Pharmaceuticals and has received research funding from Aelis Farma. MLG has served as a member of the Scientific Advisory Board to Johnson & Johnson; he has also consulted with both the World Health Organization and Campaign for Tobacco Free Kids on toxicity of tobacco products and tobacco control products; MLG is also a Member of the IASLC Tobacco Control and Smoking Cessation Committee; and a leadership role with the American Association for Cancer Research. JD is a co-owner of Behavioral Activation Tech LLC, a small business that develops digital interventions for behavioral health treatment.

E-cigarette products (tanks and liquids) were purchased directly from NJoy; no study support provided from industry. All other authors declare no competing interests.

Acknowledgements

This study was funded by grant No. R01 CA210625 from the National Cancer Institute. JD (K23 DA045766) and TTS (K01 DA047433) were supported by the National Institute on Drug Abuse.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102142.

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