# A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

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## BACKGROUND
E-cigarettes are commonly used in attempts to stop smoking, but evidence is limited regarding their effectiveness as compared with that of nicotine products approved as smoking-cessation treatments.

## METHODS
We randomly assigned adults attending U.K. National Health Service stop-smoking services to either nicotine-replacement products of their choice, including product combinations, provided for up to 3 months, or an e-cigarette starter pack (a second-generation refillable e-cigarette with one bottle of nicotine e-liquid [18 mg per milliliter]), with a recommendation to purchase further e-liquids of the flavor and strength of their choice. Treatment included weekly behavioral support for at least 4 weeks. The primary outcome was sustained abstinence for 1 year, which was validated biochemically at the final visit. Participants who were lost to follow-up or did not provide biochemical validation were considered to not be abstinent. Secondary outcomes included participant-reported treatment usage and respiratory symptoms.

## RESULTS
A total of 886 participants underwent randomization. The 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group (relative risk, 1.83; 95% confidence interval [CI], 1.30 to 2.58; P<0.001). Among participants with 1-year abstinence, those in the e-cigarette group were more likely than those in the nicotine-replacement group to use their assigned product at 52 weeks (80% [63 of 79 participants] vs. 9% [4 of 44 participants]). Overall, throat or mouth irritation was reported more frequently in the e-cigarette group (65.3%, vs. 51.2% in the nicotine-replacement group) and nausea more frequently in the nicotine-replacement group (37.9%, vs. 31.3% in the e-cigarette group). The e-cigarette group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group (relative risk for cough, 0.8; 95% CI, 0.6 to 0.9; relative risk for phlegm, 0.7; 95% CI, 0.6 to 0.9). There were no significant between-group differences in the incidence of wheezing or shortness of breath.

## CONCLUSIONS
E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support. (Funded by the National Institute for Health Research and Cancer Research UK; Current Controlled Trials number, ISRCTN60477608.)
SWITCHING COMPLETELY FROM CIGARETTE SMOKING TO E-CIGARETTE USE WOULD BE EXPECTED TO REDUCE RISKS TO HEALTH. There are questions about risks and benefits of use of e-cigarettes for different purposes, but an important clinical issue is whether e-cigarette use in a quit attempt facilitates success, particularly as compared with the use of nicotine-replacement therapy.

A Cochrane review showed that e-cigarettes with nicotine were more effective for smoking cessation than nicotine-free e-cigarettes. A trial that compared e-cigarettes with nicotine patches for smoking cessation used cartridge e-cigarettes with low nicotine delivery and no face-to-face contact. It showed similar low efficacy for both treatments. (For further details of previous trials, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) Our trial evaluated the 1-year efficacy of refillable e-cigarettes as compared with nicotine replacement when provided to adults seeking help to quit smoking and combined with face-to-face behavioral support.

**METHODS**

**DESIGN AND OVERSIGHT**

We conducted a two-group, pragmatic, multicenter, individually randomized, controlled trial. National Health Service (NHS) stop-smoking services are available free across the United Kingdom. This trial was conducted in three service sites from May 2015 through February 2018. The Health and Lifestyle Research Unit that delivers the service for two London boroughs (Tower Hamlets and City of London), along with the Leicester and East Sussex services, recruited participants and delivered the interventions. Participating services included trial information in their advertising. Participants were also recruited through social media. Adult smokers were invited to participate if they were not pregnant or breastfeeding, had no strong preference to use or not to use nicotine replacement or e-cigarettes, and were currently not using either type of product.

The trial was approved by the National Research Ethics Service (reference number, 14/LO/2235). Collective unblinded data were seen only for the purposes of the meetings of the data monitoring and ethics committee. Data analyses were conducted with blinding to treatment assignments. All the authors contributed to the trial design, participated in the interpretation of the data, vouch for their completeness and accuracy, and made the decision to submit the manuscript for publication. All the authors vouch for the fidelity of the trial to the protocol, available at NEJM.org.

**PROCEDURES**

Smokers were provided with trial information, prescreened for eligibility, and, if eligible, invited to a baseline session. There, eligibility was confirmed, written informed consent and baseline data were obtained, and participants set up their quit date (normally the following week). Randomization took place on the quit date to limit differential dropout. Randomization sequences (1:1 ratio in permuted blocks of 20, stratified according to trial site) were generated with the use of a pseudorandom number generator in Stata software and were embedded into an application that only revealed the next treatment assignment once a participant had been entered into the database.

Product use started immediately after randomization. All the participants received the same multisession behavioral support as per U.K. stop-smoking service practice. This support involved weekly one-on-one sessions with local clinicians, who also monitored expired carbon monoxide levels for at least 4 weeks after the quit date.

Participants were contacted by telephone at 26 and 52 weeks. Interviewers asked about product use and thus were aware of the treatment assignments. Participants who reported abstinence or a reduction in smoking of at least 50% at 52 weeks were invited back to provide a carbon monoxide reading. Participants were compensated £20 ($26 U.S.) for their travel and time at the 52-week validation visit.

**Nicotine-Replacement Group**

Participants were informed about the range of nicotine-replacement products (patch, gum, lozenges, nasal spray, inhalator, mouth spray, mouth strip, and microtabs) and selected their preferred product. Use of combinations was encouraged, typically the patch and a faster-acting oral product. Participants were also free to switch
products. The way that nicotine replacement was provided differed slightly among trial sites (see the Supplementary Appendix). Supplies were provided for up to 3 months, as per standard practice. The cost to the NHS of a 3-month supply of a single nicotine-replacement product is currently approximately £120 ($159 U.S.).

**E-Cigarette Group**

A starter pack, called One Kit (Aspire, U.K. Ecig Store), was provided to facilitate initial use and teach participants how to use refillable e-cigarette products, along with one 30-ml bottle of Tobacco Royale flavor e-liquid purchased from U.K. Ecig Store, containing nicotine at a concentration of 18 mg per milliliter. The kit had a 2.1-ohm atomizer and 650-mAh battery. During the trial, the company discontinued this kit, so One Kit 2016 (Innokin, U.K. Ecig Store), with a 1.5-ohm atomizer and 1000-mAh battery, was used for 42 participants. Participants were asked to purchase their future e-liquid online or from local vape shops and to buy a different e-cigarette device if the one supplied did not meet their needs. They were encouraged to experiment with e-liquids of different strengths and flavors. Those who were unable to obtain their own supply were provided with one further 10-ml bottle, but this was not offered proactively. Participants received oral and written information on how to operate the e-cigarette.

The original One Kit, including five atomizers, U.K. adapter, spare battery, and e-liquid, was purchased wholesale for £19.40 ($26 U.S.). The cost of One Kit 2016, including the same extras, was £30.25 ($40 U.S.).

Participants in the e-cigarette group and those in the nicotine-replacement group were asked to sign a commitment to not use the non-assigned treatment for at least 4 weeks after their quit date. This was to minimize contamination between the trial groups.

**MEASURES**

At trial visits, the following data were recorded: smoking status, expired carbon monoxide level (at baseline, 4 weeks, and 52 weeks), use and ratings of trial products, ratings of withdrawal symptoms (weeks 1 through 6), adverse reactions (presence or absence of nausea, sleep disturbance, and throat or mouth irritation), and respiratory symptoms (presence or absence of shortness of breath, wheezing, cough, and phlegm). The Supplementary Appendix provides further details of trial measures.

The primary outcome was 1-year sustained abstinence, calculated in accordance with the Russell Standard as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date, validated biochemically by an expired carbon monoxide level of less than 8 ppm at 1-year follow-up and not contradicted by any previous self-report or validation result. Carbon monoxide validation is the standard measure in trials assessing nicotine-containing products (see the Supplementary Appendix). Participants who died (one in each group) were excluded. Participants who were lost to follow-up or did not provide biochemical validation were classified as not being abstinent in the primary analysis.

Secondary abstinence outcomes included sustained abstinence from 26 to 52 weeks, at 4 weeks, and at 26 weeks and the percentage of participants without sustained abstinence from 26 to 52 weeks who reduced their cigarette consumption by at least 50%. We also assessed 7-day abstinence at 4, 26, and 52 weeks. In addition, we compared the trial groups with respect to relapse rate and time to relapse and with respect to the measures listed above.

**STATISTICAL ANALYSIS**

We calculated that a sample of 886 participants would provide the trial with 95% power (at a two-sided alpha level of 0.05) if the true percentages of 1-year abstinence were 23.8% in the e-cigarette group and 14.0% in the nicotine-replacement group (relative risk, 1.7). Since trial setup, the abstinence rate in stop-smoking service clinics declined to 10%, but the sample of 886 participants would provide 85% power if the percentages were 17.0% and 10.0% in the respective groups.

The primary and secondary abstinence outcomes were analyzed by regression of smoking status at each time point onto trial group. Primary analyses were adjusted for trial center to account for the stratification factor. In sensitivity analyses, each model was further adjusted for baseline covariates selected with the use of stepwise regression. Binary regressions were conducted by means of the generalized linear model.
with binomial distribution and logarithmic link to estimate the relative risk for e-cigarettes as compared with nicotine-replacement therapy.

To assess the effect of missing data on the primary outcome, we conducted four prespecified sensitivity analyses, which excluded participants who did not attend at least one behavioral-support session, excluded participants who used the nonassigned product for at least 5 consecutive days, excluded participants who did not complete the 52-week follow-up, and imputed missing information with the use of multiple imputation by chained equations. Missing data were imputed for 136 participants in each group, and 50 data sets were imputed.

We also estimated mean differences and 95% confidence intervals between trial groups in product ratings and in change scores between baseline and follow-up time points in withdrawal symptoms, as well as between-group differences in the percentage of participants who had adverse reactions or respiratory symptoms, using binomial regression with adjustment for trial center (see the statistical analysis plan, available with the protocol at NEJM.org). Analyses were conducted with the use of Stata software, version 15 (StataCorp).

**RESULTS**

**PARTICIPANTS**

A total of 2045 clients of stop-smoking services were screened, and 886 underwent randomization (439 to the e-cigarette group and 447 to the nicotine-replacement group). Of the randomly assigned participants, 78.8% completed the 52-week follow-up (Fig. 1). The sample was composed largely of middle-aged smokers, with 40.7% entitled to free prescriptions (a marker of social disadvantage or poor health) (Table 1, and Table S1 in the Supplementary Appendix).

**EFFECTS OF TREATMENT ON ABSTINENCE**

The rate of sustained 1-year abstinence was 18.0% in the e-cigarette group and 9.9% in the nicotine-replacement group (relative risk, 1.83; 95% confidence interval [CI], 1.30 to 2.58; \( P<0.001 \)) (Table 2). The absolute difference in the 1-year abstinence rate between the two groups was 8.1 percentage points, resulting in a number needed to treat for one additional person to have sustained abstinence of 12 (95% CI, 8 to 27). The result did not change substantially in the four sensitivity analyses (relative risk, 1.75 to 1.85; \( P<0.001 \) for all comparisons) (Table S2 in the Supplementary Appendix). Abstinence rates were higher in the e-cigarette group than in the nicotine-replacement group.
E-Cigarettes vs. Nicotine-Replacement Therapy

We conducted a post hoc analysis, in which participants with 1-year abstinence who used nonassigned products (see the Supplementary Appendix) were removed from the sample (3% [2 of 79] in the e-cigarette group were using nicotine replacement and 20% [9 of 44] in the nicotine-replacement group were using e-cigarettes). This resulted in a 1-year abstinence rate of 17.7% in the e-cigarette group, as compared with 8.0% in the nicotine-replacement group (relative risk, 2.21; 95% CI, 1.52 to 3.22).

Among participants in whom full abstinence
was not achieved, more had a carbon monoxide–validated reduction of smoking by at least 50% in the e-cigarette group than in the nicotine-replacement group (Table 2). Time to relapse and relapse rates at 52 weeks among participants with sustained abstinence at 4 weeks did not differ substantially between the two trial groups (hazard ratio for time to relapse, 1.14; 95% CI, 0.96 to 1.34; relative risk of relapse at 52 weeks, 1.27; 95% CI, 0.93 to 1.73).

TREATMENT ADHERENCE AND RATINGS AND EFFECTS ON WITHDRAWAL SYMPTOMS

Overall adherence was similar in the two groups, but e-cigarettes were used more frequently and for longer than nicotine replacement (Table 3). In the nicotine-replacement group, 88.1% of participants used nicotine-replacement combinations. In the e-cigarette group, practically all participants used refillable e-cigarettes (Table S4 in the Supplementary Appendix).

Among participants with 1-year abstinence, 80% (63 of 79) were using e-cigarettes at 52 weeks in the e-cigarette group and 9% (4 of 44) were using nicotine replacement in the nicotine-replacement group. Further details of product use (including the use of nonassigned products) are provided in the Supplementary Appendix, including Tables S4 and S5.

Both e-cigarettes and nicotine-replacement products were perceived to be less satisfying than cigarettes. However, e-cigarettes provided greater satisfaction and were rated as more helpful to refrain from smoking than nicotine-replacement products (Table S6 in the Supplementary Appendix).

Among participants with abstinence at 1 week after their quit date as well as participants with abstinence at 4 weeks, those in the e-cigarette group had less severe urges to smoke than did those in the nicotine-replacement group (Table 4). They also reported a smaller increase from baseline in irritability, restlessness, and inability to concentrate than those in the nicotine-replacement group during the first week of abstinence. Between-group differences in hunger and depression were in the same direction but less substantial. By week 4, participants in either group who were abstinent reported little withdrawal discomfort (Table S7 in the Supplementary Appendix).

**Table 3. Attendance and Treatment Adherence.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>E-Cigarettes (N = 438)</th>
<th>Nicotine Replacement (N = 446)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of contacts completed (IQR)*</td>
<td>5 (4–5)</td>
<td>5 (4–5)</td>
</tr>
<tr>
<td>Maximum no. of contacts completed — no. of participants (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (1.8)</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>2</td>
<td>25 (5.7)</td>
<td>40 (9.0)</td>
</tr>
<tr>
<td>3</td>
<td>38 (8.7)</td>
<td>45 (10.1)</td>
</tr>
<tr>
<td>4</td>
<td>86 (19.6)</td>
<td>106 (23.8)</td>
</tr>
<tr>
<td>5</td>
<td>281 (64.2)</td>
<td>245 (54.9)</td>
</tr>
</tbody>
</table>

* The maximum number of contacts was five: at the target quit date, 1 week, 4 weeks, 26 weeks, and 52 months.
† For use of assigned products, missing information was imputed from the information from the next weekly behavioral-support consultation, if available (e.g., for missing information at consultation 3, information was taken from consultation 4).
‡ The results were similar for weeks 1 through 4.
Two participants died during the trial. One died from ischemic heart disease in the e-cigarette group and one from traumatic spine injury in the nicotine-replacement group.

There were 27 serious adverse events in the e-cigarette group and 22 in the nicotine-replacement group (Table S8 in the Supplementary Appendix). No serious adverse event in either group was classified by the trial clinician as being related to product use, but we noted 1 respiratory event in the nicotine-replacement group and 5 in the e-cigarette group (2 in participants who were smoking and not vaping, 2 in participants who were smoking and vaping, and 1 in a participant whose status with respect to smoking and vaping was not known) (see the Supplementary Appendix).

Of the prespecified adverse reactions of interest, nausea was reported more frequently in the nicotine-replacement group (37.9%, vs. 31.3% in the e-cigarette group) and throat or mouth irritation more frequently in the e-cigarette group (65.3%, vs. 51.2% in the nicotine-replacement group). There was little difference between the two groups in the percentage of participants reporting severe nausea (6.6% in the e-cigarette group and 6.5% in the nicotine-replacement group) or severe throat or mouth irritation (5.9% and 3.9%, respectively) (Tables S9 and S10 in the Supplementary Appendix).

Regarding the prespecified respiratory symptoms of interest, the incidence of cough and phlegm production declined in both trial groups from baseline to 52 weeks. However, among participants who reported cough or phlegm at baseline, significantly more were symptom-free at the 52-week follow-up in the e-cigarette group than in the nicotine-replacement group (Table 5). To determine whether this was due to the higher abstinence rate in the e-cigarette group, we ran an exploratory analysis that controlled for

| Table 4. Urges to Smoke in Participants with Abstinence at 1 Week or 4 Weeks after Quit Date.* |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Variable                        | E-Cigarettes (N = 158) | Nicotine Replacement (N = 131) | Mean Difference (95% CI) | E-Cigarettes (N = 186) | Nicotine Replacement (N = 132) | Mean Difference (95% CI) |
|                                 |                        |                            |                              |                            |                            |                              |
| Score for frequency of urge     | 2.5±1.1               | 2.8±0.9                    | -0.4 (-0.6 to -0.1)           | 1.9±0.9                    | 2.2±0.8                    | -0.3 (-0.5 to -0.1)           |
| Score for strength of urge      | 2.7±1.1               | 3.2±1.0                    | -0.5 (-0.7 to -0.2)           | 2.1±1.1                    | 2.4±1.0                    | -0.3 (-0.6 to -0.1)           |
| Composite urge score            | 2.6±1.0               | 3.0±0.9                    | -0.4 (-0.6 to -0.2)           | 2.0±1.0                    | 2.3±0.9                    | -0.3 (-0.5 to -0.1)           |

* Plus–minus values are means ±SD. Scores for frequency of urge ranged from 1 (not at all) to 6 (all the time). Scores for strength of urge ranged from 1 (no urges) to 6 (extremely strong). The composite score (range, 1 to 6, with higher scores indicating more severe urges) is an average of the frequency and strength scores.

| Table 5. Respiratory Symptoms at Baseline and at 52 Weeks.* |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Symptom                         | E-Cigarettes (N = 315) | Nicotine Replacement (N = 279) | Relative Risk (95% CI)† |
|                                 | Baseline | 52 Weeks | Baseline | 52 Weeks |                    |
|                                 | number (percent) | number (percent) | number (percent) | number (percent) | Relative Risk (95% CI)† |
| Shortness of breath             | 120 (38.1) | 66 (21.0) | 92 (33.0) | 64 (22.9) | 0.9 (0.7–1.1) |
| Wheezing                        | 102 (32.4) | 74 (23.5) | 86 (30.8) | 59 (21.1) | 1.1 (0.8–1.4) |
| Cough                           | 173 (54.9) | 97 (30.8) | 144 (51.6) | 111 (39.8) | 0.8 (0.6–0.9) |
| Phlegm                          | 137 (43.5) | 79 (25.1) | 121 (43.4) | 103 (36.9) | 0.7 (0.6–0.9) |

* Symptoms were assessed by asking whether participants had the symptom (yes or no).
† Relative risk was calculated by means of logistic regression. Symptoms at 52 weeks were regressed onto trial group, with adjustment for baseline symptoms and trial center.
abstinence status at 52 weeks. This did not change the results (relative risk for cough, 0.8; 95% CI, 0.6 to 0.9; relative risk for phlegm, 0.7; 95% CI, 0.6 to 0.9).

**DISCUSSION**

E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy in this randomized trial. This is particularly noteworthy given that nicotine replacement was used under expert guidance, with access to the full range of nicotine-replacement products and with 88.1% of participants using combination treatments.11

Our trial showed a stronger effect of e-cigarettes than previous trials.5,12,13 This could be due to the inclusion of smokers seeking help in quitting, the provision of face-to-face support, and the use of refillable e-cigarettes with free choice of e-liquids. Previous trials provided limited or no face-to-face support and used first-generation cartridge products. Refillable devices are generally more efficient at nicotine delivery.14

The trial provides some indications of why e-cigarettes had better results than nicotine-replacement treatments. As in previous studies,5,15 e-cigarettes were more effective in alleviating tobacco withdrawal symptoms and received better ratings than nicotine-replacement therapy. They may also have allowed better tailoring of nicotine dose to individual needs.

The rate of continuing e-cigarette use was fairly high. This can be seen as problematic if e-cigarette use for a year signals ongoing long-term use, which may pose as-yet-unknown health risks. On the positive side, ongoing e-cigarette use may ameliorate withdrawal symptoms, such as constipation,16 mouth ulcers,17 and weight gain,18 and continue to provide some of the positive subjective effects previously derived from smoking.19 Provided that ongoing e-cigarette use has similar effects to long-term nicotine-replacement use, for heavy smokers with a high risk of relapse, long-term e-cigarette use may also assist with preventing relapse.20 Among participants in our trial in whom full abstinence was not achieved, those in the e-cigarette group were more likely to reduce their smoke intake than those in the nicotine-replacement group, but it is unclear whether this affects future abstinence.

E-cigarettes caused more throat or mouth irritation, and nicotine replacement caused more nausea; these effects were mostly mild. There were mixed signals regarding the effects of e-cigarettes on the respiratory system. More participants in the e-cigarette group than in the nicotine-replacement group reported respiratory serious adverse events, although the difference was not significant and some of the affected participants were not vaping. Meanwhile, we detected positive effects of e-cigarette use on some respiratory outcomes. Similar positive effects were reported previously. A switch to e-cigarettes was accompanied by a reduction in respiratory infections in an online survey,21 and two case studies described nonsmokers with chronic throat and nose infections that resolved after they started to vape. Antibacterial effects of propylene glycol and glycerin were suggested as possible explanations.22,23 (For more on e-cigarettes and the respiratory system, see the Supplementary Appendix.)

The trial had several limitations. Product assignments could not be blinded. Positive expectations have limited effects on long-term abstinence, but if nicotine replacement was seen as an inferior option, participants in the nicotine-replacement group could have put less effort into their quit attempt than those in the e-cigarette group. We tried to limit expectation effects by recruiting only participants with no strong product preference. Abstinence rates in the nicotine-replacement group were also at least as high as in usual practice24 (see the Supplementary Appendix). Nevertheless, lack of blinding could affect the results. Carbon monoxide validation detects smoking only over the past 24 hours, so there may have been some false negative results. Several participants in the nicotine-replacement group used e-cigarettes during the trial, but this would dilute rather than amplify any effects of e-cigarettes. The 1-year follow-up rate of 79% was similar to the rates of 78%,19 79%,3 and 75%-20 observed in other studies involving the same general population and setting. Achieving higher follow-up rates among smokers engaged in face-to-face treatment is difficult, because they tend to feel embarrassed if they do not quit, and some avoid further contact. Multiple imputation showed consistent results; nevertheless, incomplete follow-up represents another limitation of the trial.

The findings are likely to be valid for depen-
dent smokers who seek help but may not be generalizable to smokers who are less dependent or who try e-cigarettes for reasons other than quitting smoking. In addition, they may not be generalizable to less effective first-generation e-cigarettes. Moreover, not all service clients want e-cigarettes. In a previous study, 69% accepted the offer of an e-cigarette starter pack. (For comparison, 57% of service clients opt for nicotine replacement and 25% for varenicline.)

Further trials are needed to determine whether our results generalize outside the U.K. services. In addition, e-cigarette studies are needed that compare different levels of support. This is important for focusing public health messages on either encouraging smokers to switch to e-cigarette use within support services or recommending use with less intensive or no support.

In our trial, refillable e-cigarettes had greater efficacy than nicotine-replacement therapy, even though nicotine replacement was provided in combinations and under expert guidance.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES