ORIGINAL ARTICLE

# Electronic Nicotine-Delivery Systems for Smoking Cessation

Reto Auer, M.D., Anna Schoeni, Ph.D., Jean-Paul Humair, M.D., M.P.H., Isabelle Jacot-Sadowski, M.D., Ivan Berlin, M.D., Ph.D., Mirah J. Stuber, M.D., Moa Lina Haller, M.D., Rodrigo Casagrande Tango, M.D., M.P.H., Anja Frei, Ph.D., Alexandra Strassmann, Ph.D., Philip Bruggmann, M.D., Florent Baty, Ph.D., Martin Brutsche, M.D., Ph.D., Kali Tal, Ph.D., Stéphanie Baggio, Ph.D., Julian Jakob, M.D., Nicolas Sambiagio, Ph.D., Nancy B. Hopf, Ph.D., Martin Feller, M.D., Nicolas Rodondi, M.D., and Aurélie Berthet, Ph.D.

## ABSTRACT

### BACKGROUND

Electronic nicotine-delivery systems — also called e-cigarettes — are used by some tobacco smokers to assist with quitting. Evidence regarding the efficacy and safety of these systems is needed.

### METHODS

In this open-label, controlled trial, we randomly assigned adults who were smoking at least five tobacco cigarettes per day and who wanted to set a quit date to an intervention group, which received free e-cigarettes and e-liquids, standard-of-care smoking-cessation counseling, and optional (not free) nicotine-replacement therapy, or to a control group, which received standard counseling and a voucher, which they could use for any purpose, including nicotine-replacement therapy. The primary outcome was biochemically validated, continuous abstinence from smoking at 6 months. Secondary outcomes included participant-reported abstinence from tobacco and from any nicotine (including smoking, e-cigarettes, and nicotine-replacement therapy) at 6 months, respiratory symptoms, and serious adverse events.

### RESULTS

A total of 1246 participants underwent randomization; 622 participants were assigned to the intervention group, and 624 to the control group. The percentage of participants with validated continuous abstinence from tobacco smoking was 28.9% in the intervention group and 16.3% in the control group (relative risk, 1.77; 95% confidence interval, 1.43 to 2.20). The percentage of participants who abstained from smoking in the 7 days before the 6-month visit was 59.6% in the intervention group and 38.5% in the control group, but the percentage who abstained from any nicotine use was 20.1% in the intervention group and 33.7% in the control group. Serious adverse events occurred in 25 participants (4.0%) in the intervention group and in 31 (5.0%) in the control group; adverse events occurred in 272 participants (43.7%) and 229 participants (36.7%), respectively.

### CONCLUSIONS

The addition of e-cigarettes to standard smoking-cessation counseling resulted in greater abstinence from tobacco use among smokers than smoking-cessation counseling alone. (Funded by the Swiss National Science Foundation and others; ESTxENDS ClinicalTrials.gov number, NCT03589989.)

From the Institute of Primary Health Care (BIHAM) (R.A., A. Schoeni, M.J.S., M.L.H., K.T., S.B., J.J., M.F., N.R.) and the Departments of General Internal Medicine (M.J.S., N.R.) and Pediatrics (J.J.), Bern University Hospital (Inselspital), University of Bern, Bern, the University Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne (R.A., I.J.-S., I.B., N.S., N.B.H., A.B.), the Department of Primary Care Medicine, University Hospitals of Geneva, Geneva (J.-P.H., R.C.T.), the Epidemiology, Biostatistics and Prevention Institute, University of Zurich (A.F., A. Strassmann), Arud Center for Addiction Medicine (P.B.), and the Institute of Primary Care, University and University Hospital of Zurich (P.B.), Zurich, the Lung Center, Kantonsspital St. Gallen, St. Gallen (F.B., M.B.), the University of Basel, Basel (F.B., M.B.), and the Population Health Laboratory, University of Fribourg, Fribourg (S.B.) — all in Switzerland; and the Department of Medical Pharmacology, Hôpital Pitié–Salpêtrière, Sorbonne Université, Paris (I.B.). Dr. Auer can be contacted at reto.auer@unibe.ch or at the Institute of Primary Health Care (BIHAM), University of Bern, Mittelstrasse 43, CH-3012 Bern, Switzerland.

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Electronic nicotine-delivery systems — also called e-cigarettes — are battery-powered devices that reproduce many features of tobacco cigarettes; as such, they are a potential smoking-cessation aid.[1] However, the attributes that make e-cigarettes potentially attractive for smoking cessation may also encourage prolonged use,[1,2] so rigorous evaluation of their safety and toxicologic profile is an urgent requirement.

A sufficiently powered randomized trial and a systematic review of randomized, controlled trials showed that e-cigarettes were more effective for tobacco smoking cessation than nicotine-replacement therapy,[1,3] but evidence is limited regarding the efficacy of e-cigarettes as compared with standard-of-care smoking-cessation counseling and regarding the safety of e-cigarettes as measured by the incidence of adverse events and serious adverse events associated with their use.[1] Few trials have systematically collected data on prespecified safety outcomes and confirmed them by reviewing participants' medical records.[1,3] When tobacco smokers quit, smoking-associated respiratory symptoms such as cough and phlegm production are likely to diminish,[4] but whether quitting with the use of e-cigarettes also relieves these respiratory symptoms is unclear.

E-cigarettes deliver lower levels of toxic compounds than conventional tobacco cigarettes,[5-9] but few randomized, controlled trials have verified whether e-cigarettes for smoking cessation are associated with a reduction in exposure to nicotine and other tobacco-related and smoke-related toxic substances, though levels of these substances can be measured with urinary biomarkers.[9-11]

We therefore conducted the Efficacy, Safety and Toxicology of Electronic Nicotine Delivery Systems as an Aid for Smoking Cessation (ESTxENDS) randomized, controlled trial to assess the efficacy and safety of e-cigarettes in addition to standard care as compared with standard care alone with respect to abstinence from tobacco smoking at 6 months.

## Methods

### Design and Oversight

We conducted an open-label, randomized, controlled trial at five sites across Switzerland. From July 2018 through June 2021, we recruited participants by means of free and paid advertisements in the lay press and on social media and by advertising in health care facilities and on public transport. Adults 18 years of age or older who had smoked at least five cigarettes per day for at least 12 months and wanted to quit smoking within 3 months after enrollment were eligible to participate. We excluded persons who were pregnant or breast-feeding, persons who had used nicotine-replacement therapy or another smoking-cessation drug in the previous 3 months, and persons who had regularly used e-cigarettes or tobacco-heating systems in the previous 3 months (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The local ethics committee at each participating site approved the trial. Personnel who collected and analyzed the data were aware of the participants' group assignments. The data and safety monitoring board first met in 2020 and reviewed procedures for collecting adverse events and serious adverse events. An independent adjudication committee reviewed serious adverse events that were documented in participants' medical records (see the Supplementary Appendix for details). Site investigators gathered the data. The second author analyzed the data and vouches for the accuracy and completeness of the data and the integrity of the analyses. The first author wrote the first draft of the manuscript. All authors interpreted the data, agreed to submit the manuscript for publication, and vouch for the fidelity of the trial to the protocol, available at NEJM.org. The funding bodies had no role in the trial design; the collection, monitoring, analysis, or interpretation of the data; or the writing of the manuscript. There was no industry involvement in the trial.

### Procedures

Persons who were interested in participating in the trial contacted nurses who were available at each site to prescreen volunteers for eligibility. Eligible participants were asked to specify their target quit date, had a baseline visit scheduled a week before that date, and were sent trial materials before their visit. At the baseline visit, the nurses confirmed eligibility and collected written consent forms and baseline data. An automated, centralized, online randomization system in a protected environment at the Clinical Trials Unit in Bern, Switzerland, then generated randomization sequences in a 1:1 ratio.

Nurses and participants were aware of the group assignment.

Participants were invited to an in-person clinic visit scheduled 6 months after their target quit date. If they missed this visit, trial nurses collected data through telephone calls, mail, or email. After three unsuccessful contact attempts, trial nurses contacted up to two relatives and the participant's general practitioner, if the participant had voluntarily provided this information, and collected available data on smoking status and serious and nonserious adverse events from these sources.

### CONTROL GROUP

Trial nurses provided standard-of-care smoking-cessation counseling, which involved cognitive behavioral therapy, motivational interviewing, and shared decision making for the use of drugs that support smoking cessation, including nicotine-replacement therapy and smoking-cessation medications; the recommendations were adapted to the nicotine dependence of the participants (see the Supplementary Appendix).[12,13] Participants were counseled in person at the baseline visit, by telephone at their target quit date, and by telephone at weeks 1, 2, 4, and 8 after their target quit date. Participants who were assigned to the control group received vouchers worth 50 Swiss francs ($50 in U.S. dollars) at the baseline visit, which they could use for any purpose, including the purchase of nicotine-replacement therapy.

### INTERVENTION GROUP

In addition to standard smoking-cessation counseling (including the optional use of nicotine-replacement therapy, the in-person session, and five telephone calls), which we adapted to the context of the intervention, participants in the intervention group received two e-cigarette starter kits (Innokin Endura T20-S) and five spare 0.8-ohm coils (enabling a fixed wattage of 16 to 18 watts with a 1500-milliampere-hour internal lithium-polymer battery) at the baseline visit, during which trial nurses showed the participants how to use and charge the device, fill it with e-liquid, and change the coil every 2 weeks. Participants could choose among six flavors (two tobacco, one menthol, and three fruity) and four nicotine concentrations (19.6 mg, 11 mg, 6 mg, and 0 mg per milliliter). E-liquids contained propylene glycol, vegetable glycerin, medical-quality free-base nicotine, alcohol, and flavoring. All e-liquids had a ratio of propylene glycol to vegetal glycerin of 76:24. At the baseline visit, participants could sample the 24 e-liquid options, comprising all the flavors and nicotine combinations, which were presented to them on an e-liquid testing board. They could then choose the flavor and nicotine concentration they preferred. Trial nurses gave participants no more than 10 e-liquid bottles at the end of this baseline visit. Participants could use e-cigarettes as desired and order e-liquids through the trial nurses whenever and in whatever amount they wanted, in whatever nicotine concentrations or flavors they preferred for 6 months. Nurses advised participants to use only the e-liquids they received through the trial (see the Supplementary Appendix).

### MEASURES

At baseline and the 6-month follow-up visit, participants completed questionnaires and underwent several clinical tests. Information was obtained regarding demographic variables, smoking history, smoking status, expired carbon monoxide level, withdrawal symptoms, and respiratory symptoms. Trial nurses documented adverse events and serious adverse events at the 6-month follow-up visit and each telephone contact; participants could also report these events to the research team at any time. We defined serious adverse events as any event that resulted in hospitalization, substantial incapacity, or death, or an event that led to interventions to prevent one of these outcomes (see the Supplementary Appendix for details).[14-16] We used the COPD [chronic obstructive pulmonary disease] Assessment Test to assess participants' respiratory symptoms; the score is the sum of points from an 8-item questionnaire, on which each item ranges from 0 to 5 (maximum, 40 points), with higher scores indicating worse symptoms. Participants were told to collect their first morning urine and bring the filled bags to their examination.

### OUTCOMES

The primary outcome was continuous abstinence from tobacco smoking at 6 months as measured by participant report of no cigarette smoking after their target quit date, with biochemical

validation by an anabasine level of less than 3 ng per milliliter in a urine sample.[17-19] If anabasine data were unavailable, we validated abstinence by an exhaled carbon monoxide level of 9 ppm or lower. In the primary analysis, we classified participants who withdrew from the trial or were lost to follow-up or who lacked biochemical validation as not having abstained.[18]

Secondary outcomes included sustained abstinence from tobacco smoking for 6 months (with allowance of up to 5 cigarettes or a 2-week grace period after their target quit date)[18] and abstinence from tobacco smoking in the 7 days before the 6-month follow-up visit, with biochemical validation and without biochemical validation. We also present data on participant-reported exposure to e-cigarettes and tobacco smoking in the 7 days before the 6-month visit and on nicotine-replacement therapy within the 24 hours before the 6-month visit. Details regarding these and other secondary outcomes, including antibiotic use and withdrawal symptoms, are provided in the Supplementary Appendix.

### STATISTICAL ANALYSIS

We calculated that a sample of 1114 participants would provide the trial with 90% power (at a two-sided alpha error of 0.05) if the percentage of participants who abstained from smoking for 6 months would be 19% in the intervention group and 12% in the control group (relative risk, 1.6; absolute difference in abstinence, 7 percentage points). We assumed that 5% of the participants would be lost to follow-up and that 5% of participants in the control group would choose to purchase e-cigarettes on their own, despite the recommendation not to do so (and thus crossover from the control group to the intervention group would occur), so we increased our sample size by 5% (59 tobacco smokers) and aimed to recruit 1173 tobacco smokers.

We analyzed the primary and secondary abstinence outcomes using a log-binomial regression model to compute risk ratios of smoking status in the comparison of the trial groups at 6 months. In sensitivity analyses, we further adjusted the models for baseline covariates and computed the inverse probability of censoring weights in the multivariable regression models to assess the effect of missing data on the outcome. Variables that were included in the multivariable-adjusted model and the inverse probability of censoring weights models were prespecified before the analyses were begun. We also conducted a tipping-point analysis to assess the effect of missing primary outcome data on the main efficacy results.[20] We estimated between-group differences in the percentage of participants who had serious or nonserious adverse events and in the percentage of participants who reported antibiotic use. The widths of the confidence intervals for the secondary outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing. Participants who wanted to use nicotine-replacement therapy had to purchase it in a pharmacy and pay for it themselves. Participants who wanted prescription drug therapy (varenicline or bupropion) were encouraged to consult their primary care physician or another health care professional who could prescribe the drug. We classified participants into the following exposure groups: "tobacco abstainers" reported no use of tobacco cigarettes, regardless of their use of e-cigarettes; "tobacco and e-cigarette abstainers" reported no use of tobacco cigarettes or e-cigarettes; "nicotine abstainers" reported no use of tobacco cigarettes, e-cigarettes with nicotine, or nicotine-replacement therapy; "exclusive e-cigarette users" reported no use of tobacco cigarettes but the use of e-cigarettes; "dual users" reported the use of both tobacco cigarettes and e-cigarettes; and "exclusive smokers" reported the use of tobacco cigarettes but not e-cigarettes. We used Stata software, version 17 (StataCorp) for all analyses except the tipping-point analyses, for which we used R, version 4.3.1, TippingPoint package, version 1.2.0.

## RESULTS

### CHARACTERISTICS OF PARTICIPANTS AT BASELINE

We screened 2027 tobacco smokers and included 1246 participants in the primary analyses (622 in the intervention group and 624 in the control group) (Fig. 1 and Tables S1 and S2 in the Supplementary Appendix). Most of the participants were middle-aged; 47% identified as women (Table 1 and Tables S4 and S5). The mean (±SD) number of days from the baseline visit to the target quit date was 6.0±3.6 in the intervention group and 6.0±3.9 in the control group.

**Table 1. Characteristics of the Participants at Baseline.***

| Characteristic | Control Group (N=624) | Intervention Group (N=622) | Total (N=1246) |
|---|---|---|---|
| Median age (IQR) — yr | 39 (30–52) | 37 (28–51) | 38 (29–51) |
| Female gender identity — no. (%) | 295 (47.3) | 290 (46.6) | 585 (47.0) |
| Employed — no. (%) | 465 (74.5) | 438 (70.4) | 903 (72.5) |
| Highest educational level — no. (%) | | | |
| Obligatory school, some obligatory school, or no formal schooling† | 45 (7.2) | 50 (8.0) | 95 (7.6) |
| Secondary education | 277 (44.4) | 291 (46.8) | 568 (45.6) |
| Tertiary education | 302 (48.4) | 281 (45.2) | 583 (46.8) |
| Median age at which smoking was started (IQR) — yr‡ | 16 (15–19) | 16 (15–18) | 16 (15–19) |
| Median no. of cigarettes per day (IQR) | 15 (10–20) | 15 (10–20) | 15 (10–20) |
| At least one previous attempt to quit smoking — no. (%)‡ | 530 (84.9) | 531 (85.4) | 1061 (85.2) |
| Fagerström Test for Nicotine Dependence score‡§ | 4.4±2.3 | 4.3±2.3 | 4.3±2.3 |
| Median expired CO level (IQR) — ppm¶ | 20 (12–29) | 20 (13–29) | 20 (12–29) |

* Plus–minus values are means ±SD. CO denotes carbon monoxide, and IQR interquartile range.
† Obligatory school (i.e. compulsory school) lasts between 9 and 11 years in Switzerland, depending on local laws.
‡ Data are missing for 2 participants, 1 in each group.
§ The Fagerström Test for Nicotine Dependence consists of 6 questions that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence; scores range from 0 to 10, with higher scores indicating greater dependence.[21]
¶ Data are missing for 18 participants, 11 in the intervention group and 7 in the control group.

### PRIMARY AND SECONDARY OUTCOMES

Data on smoking status and serious adverse events at 6 months were available for 90.8% of participants (63.9% obtained at the follow-up visit; 23.4% obtained by telephone call, by email, or in a mailed questionnaire; 2.8% obtained from relatives; 0.2% obtained from the general practitioner; and 0.5% obtained from unknown sources) (Fig. 1 and Table S3). Biochemically validated, continuous abstinence from smoking at 6 months (the primary outcome) occurred in 28.9% (180 of 622) of the participants in the intervention group and in 16.3% (102 of 624) in the control group (crude relative risk, 1.77 (95% confidence interval [CI], 1.43 to 2.20) (Table 2). The absolute difference between the groups was 12.6 percentage points (95% CI, 8.0 to 17.2). Results for secondary outcomes, including continuous abstinence without biochemical validation, sustained abstinence with allowance of either a 2-week grace period or up to 5 total cigarettes, and abstinence within the 7 days before the 6-month follow-up visit with and without validation were generally consistent with the results of the primary analysis. Sensitivity analyses showed similar results (Table S6 and Fig. S3).

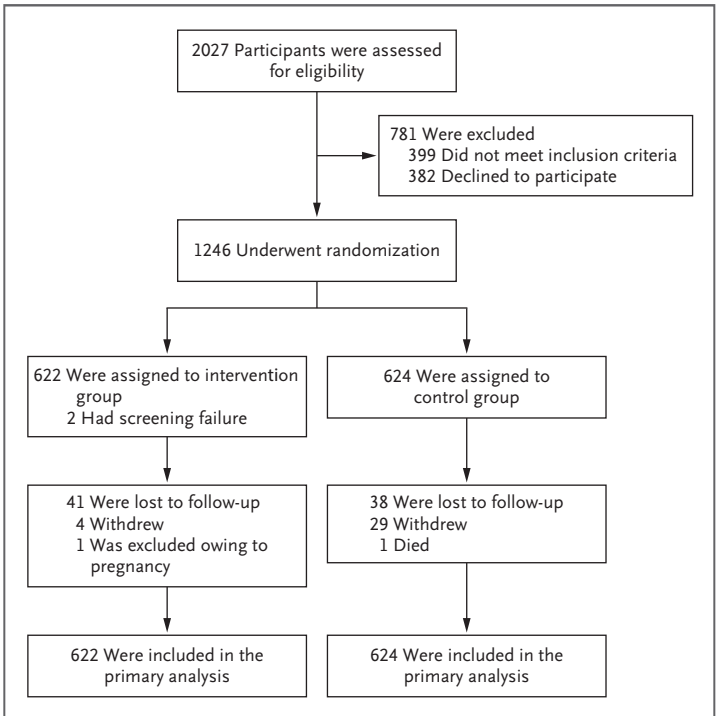


**Figure 1. Enrollment, Assignment, and Follow-up.**

**Table 2. Primary and Secondary Outcomes.**

| Outcome | Control Group N=624 | Intervention Group N=622 | Difference, Intervention vs. Control (95% CI)* | Crude Relative Risk (95% CI)† | Adjusted Relative Risk (95% CI)‡ |
|---|---|---|---|---|---|
| | *number (percent)* | | | *percentage points* | |
| Primary outcome: continuous abstinence from smoking at 6 months§ | 102 (16.3) | 180 (28.9) | 12.6 (8.0–17.2) | 1.77 (1.43–2.20) | 1.71 (1.39–2.12) |
| Secondary outcomes¶ | | | | | |
| Continuous abstinence, without biochemical validation | 146 (23.4) | 237 (38.1) | 14.7 (9.6–19.8) | 1.63 (1.37–1.94) | 1.57 (1.32–1.85) |
| Sustained abstinence allowing a 2-week grace period, with biochemical validation | 110 (17.6) | 191 (30.7) | 13.1 (8.4–17.8) | 1.74 (1.42–2.14) | 1.70 (1.39–2.08) |
| Sustained abstinence allowing up to 5 cigarettes, with biochemical validation | 109 (17.5) | 219 (35.2) | 17.7 (12.9–22.5) | 2.02 (1.65–2.46) | 1.96 (1.61–2.38) |
| Abstinence within previous 7 days, with biochemical validation | 133 (21.3) | 245 (39.4) | 18.1 (13.1–23.1) | 1.85 (1.54–2.21) | 1.74 (1.47–2.07) |
| Abstinence within previous 7 days, without biochemical validation | 200 (32.1) | 332 (53.4) | 21.3 (16.0–26.7) | 1.67 (1.45–1.91) | 1.56 (1.37–1.77) |

* The absolute difference between the groups was calculated with 95% Newcombe-hybrid-score confidence intervals.
† Relative risk was calculated with 95% Koopman confidence intervals.
‡ The adjusted relative risk was a sensitivity analysis, which was performed with the use of a multivariable adjusted model with stabilized inverse probability of censoring weights, adjusted for trial site, age, identified gender, employment status, education, age that the participant started smoking, the number of cigarettes smoked per day, previous quit attempts, and Fagerström score.
§ The primary outcome, continuous abstinence from smoking at 6 months, was defined as a participant-reported abstinence from the target quit date to the 6-month follow-up visit, validated biochemically by a urinary anabasine level of less than 3 ng per milliliter and, if not available, by an expired CO level of 9 ppm or less. P<0.001 for the chi-square test between the control and intervention groups. The percentage meeting the primary outcome was 16.3% (95% CI, 13.6 to 19.4) in the control group and 28.9% (95% CI, 25.5 to 32.6) in the intervention group (Wilson confidence intervals[22]).
¶ The widths of the confidence intervals for the secondary outcomes have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

### ADHERENCE TO SMOKING-CESSATION THERAPY AND E-CIGARETTES

A total of 90% of the participants in the intervention group and 86% in the control group participated in a follow-up telephone call 1 week after the target quit date. In the intervention group, 95.9% reported using e-cigarettes, 6.8% nicotine-replacement therapy, and 0.5% other smoking-cessation drug therapy (varenicline or bupropion) (Table S8). Participants who reported having used e-cigarettes said they had used a median of 10 ml of e-liquids throughout the week; the median nicotine concentration of the e-liquid they used was 11 mg per milliliter (Table S9). In the control group, 3.9% reported using e-cigarettes, 63.6% nicotine-replacement therapy, and 4.1% other smoking-cessation drug therapy.

### USE OF TOBACCO CIGARETTES, E-CIGARETTES, AND NICOTINE-REPLACEMENT THERAPY AT 6 MONTHS

At the 6-month follow-up visit, 84.8% of the trial participants (1056 of 1246) reported on their use of tobacco cigarettes and e-cigarettes in the 7 days before the visit and on their use of nicotine-replacement therapy in the 24 hours before the visit (Table 3). A total of 59.6% (329 of 552) of the participants in the intervention group and 38.5% (194 of 504) in the control group were "tobacco abstainers" (i.e., reported no use of tobacco cigarettes in the 7 days before the 6-month visit) (Table 3). By contrast, 20.1% in the intervention group and 33.7% in the control group were "nicotine abstainers" (abstaining from tobacco cigarettes, e-cigarettes with nicotine, and nicotine-replacement therapy).

### SAFETY

In the control group, 1 participant died during the trial. Between baseline and the 6-month follow-up visit, 25 participants (4.0%) in the intervention group and 31 participants (5.0%) in the control group had a serious adverse event (relative risk, 0.81; 95% CI, 0.48 to 1.35; unadjusted P=0.49). Of the participants in the intervention group, 272 (43.7%) reported 425 adverse events; of the participants in the control group, 229 (36.7%) reported 366 adverse events (relative risk, 1.19; 95% CI, 1.04 to 1.37; unadjusted P=0.01). Symptomatic and confirmed coronavirus disease 2019 (Covid-19) was reported by 18 participants in the intervention group and 8 participants in the control group, including 1 participant in the control group who was hospitalized. Between baseline and the 6-month follow-up visit, 54 participants (8.7%) in the intervention group reported 61 episodes of antibiotic use; 43 participants (6.9%) in the control group reported 56 episodes of antibiotic use (relative risk, 1.26; 95% CI, 0.86 to 1.85). Details on safety can be found in Tables S10 through S14.

### RESPIRATORY SYMPTOMS

At the 6-month follow-up visit, 81% of the participants in the intervention group and 66% in the control group provided data on respiratory symptoms. The mean total score on the COPD Assessment Test was 4.8±3.9 in the intervention group and 5.7±4.5 in the control group (multivariable adjusted difference in the mean total score, −0.66; 95% CI, −1.13 to −0.18). The percentage of participants who reported no cough was 41% in the intervention group as compared with 34% in the control group; 62% of the participants in the intervention group and 51% in the control group reported no phlegm; 73% and 72%, respectively, reported no chest tightness; 34% and 30% reported not feeling breathless; 95% and 93% reported no limitation in home activities; 96% and 95% reported confidence leaving home; 92% and 90% reported sound sleep; and 40% and 39% reported having a lot of energy. More details on respiratory symptoms and results for withdrawal symptoms can be found in the Supplementary Appendix.

## DISCUSSION

The addition of e-cigarettes to standard counseling that allowed the use of nicotine-replacement therapy resulted in greater abstinence from smoking than standard counseling alone, but many of those who abstained from smoking tobacco continued using e-cigarettes. The intervention resulted in more adverse events but not more serious adverse events.

The relative difference in abstinence from smoking between the randomized groups aligns with findings of previous trials, but because abstinence from smoking tobacco was high in both groups, the absolute difference was higher in our trial.[1,23,24] The percentage of participants who abstained from smoking was high in the intervention

**Table 3. Participant-Reported Use of Tobacco Cigarettes, E-cigarettes, and Nicotine-Replacement Therapy at 6 Months.***

| Participant-Reported Use | Control Group N = 504 | Intervention Group N = 552 | Difference, Intervention vs. Control |
|---|---|---|---|
| | *number (percent)* | | *percentage points* |
| No tobacco cigarettes: "tobacco abstainers" | 194 (38.5) | 329 (59.6) | 21.1 |
| No tobacco cigarettes, no e-cigarettes: "tobacco and e-cigarette abstainers" | 179 (35.5) | 62 (11.2) | –24.3 |
| With nicotine-replacement therapy | 14 (2.8) | 1 (0.2) | –2.6 |
| With smoking-cessation medication | 1 (0.2) | 0 | –0.2 |
| E-cigarettes and no tobacco cigarettes: "exclusive e-cigarette users" | 15 (3.0) | 267 (48.4) | 45.5 |
| E-cigarettes without nicotine | 5 (1.0) | 50 (9.1) | 8.1 |
| E-cigarettes with nicotine | 10 (2.0) | 217 (39.3) | 37.3 |
| E-cigarettes and nicotine-replacement therapy | 0 | 1 (0.2) | 0.2 |
| E-cigarettes and smoking-cessation medication | 0 | 0 | 0 |
| No nicotine: "nicotine abstainers"† | 170 (33.7) | 111 (20.1) | –13.6 |
| Tobacco cigarettes | 310 (61.5) | 223 (40.4) | –21.1 |
| Tobacco cigarettes and no e-cigarettes: "exclusive smokers" | 294 (58.3) | 122 (22.1) | –36.2 |
| Tobacco cigarettes and nicotine-replacement therapy | 18 (3.6) | 4 (0.7) | –2.9 |
| Tobacco cigarettes and smoking-cessation medication | 2 (0.4) | 0 | –0.4 |
| E-cigarettes and tobacco cigarettes: "dual users" | 16 (3.2) | 101 (18.3) | 15.1 |
| Without nicotine in e-cigarettes | 5 (1.0) | 10 (1.8) | 0.8 |
| With nicotine in e-cigarettes | 11 (2.2) | 91 (16.5) | 14.3 |
| With nicotine-replacement therapy | 1 (0.2) | 4 (0.7) | 0.5 |
| With smoking-cessation medication | 0 | 0 | 0 |

* Categories of exposure are based on participant-reported use of e-cigarettes and tobacco cigarettes in the 7 days before the 6-month follow-up visit, and use of nicotine-replacement therapy within the 24 hours before the visit. This table shows data for 1056 out of 1246 participants (84.7%) who provided reports of their use of tobacco cigarettes and e-cigarettes at the 6-month follow-up visit (504 of 624 participants in the control group [80.8%] and 552 of 622 participants in the intervention group [88.7%]) (Table S3). The percentages for each category of exposure were computed with the number of participants reporting their use as the denominator. Participants who reported use of e-cigarettes with missing information on nicotine concentration in the e-cigarettes (5 in the control group and 23 in the intervention group) were classified as having used e-cigarettes without nicotine.

† This category is defined as no participant-reported exposure to nicotine through tobacco cigarettes, e-cigarettes with nicotine, or nicotine-replacement therapy.

group, but the ongoing use of e-cigarettes with nicotine was also high. Electronic nicotine-delivery systems plus standard counseling may be a viable option for tobacco smokers who want to abstain from smoking without necessarily abstaining from nicotine but may be less appropriate for those who want to abstain from both tobacco and nicotine.

ESTxENDS was not powered to detect significant between-group differences in serious adverse events, but our results align with those of another large randomized, controlled trial (which failed to meet recruitment targets).[25] This trial also applied rigorous, prespecified methods to systematically collect data on serious and nonserious adverse events.[25] Our results could be pooled with those of other randomized, controlled trials that assess e-cigarettes for smoking cessation to better detect differences in serious and nonserious adverse events.[1] Participant-reported respiratory and withdrawal symptoms align with previous findings.[1,4]

The current trial had limitations. First, participants were aware of their group assignment, which created the risk that participants in the control group would be disappointed with their group assignment. We mitigated their potential disappointment by giving them a monetary voucher at

baseline, but we did not assess how they interpreted this voucher. We also did not ask participants in either group how confident they were in the efficacy of the treatment. Second, we provided free e-cigarettes and e-liquids to the intervention group but did not provide free nicotine-replacement therapy to the control group, as was done in previous trials.[2] Participants in the control group could use their voucher to purchase nicotine-replacement therapy. We did not intend to contrast a recommendation to use e-cigarettes with a recommendation to use nicotine-replacement therapy; instead, we added free e-cigarettes and e-liquids to standard counseling and compared that with standard counseling, which ordinarily includes recommendations for nicotine-replacement therapy and further smoking-cessation drugs. Third, we provided participants with free e-liquids for 6 months before conducting the end-of-treatment assessment. Our current results do not predict whether the primary outcome will be sustained over subsequent visits, so we plan to continue follow-up at 12, 24, and 60 months. Fourth, more biochemical-validation data than participant-report data were missing, and there were more missing data in the control group than in the intervention group. The results of the tipping-point analyses suggest that our main conclusions would probably remain unchanged if we had had a complete data set on the primary outcome. However, our primary analyses might have overestimated the relative risk difference between randomized groups because we followed guidelines for reporting smoking-cessation trials: we categorized participants with missing outcome data as nonabstinent from smoking.[18] Fifth, we tested the intervention in an ambulatory health care setting in Switzerland, so readers should be cautious in assuming that the results will be similar in other settings. Sixth, we did not adjust the widths of the confidence intervals for multiplicity for our secondary outcomes, so these intervals should not replace hypothesis testing.

The addition of e-cigarettes to standard counseling resulted in greater abstinence from tobacco among smokers than standard counseling alone.

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

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