Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial

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Summary

Background Combination nicotine replacement therapy shows additive cessation benefits. We aimed to find out the effectiveness of combining nicotine patches with an e-cigarette (with and without nicotine) on six-month smoking abstinence.

Methods We did a pragmatic, three-arm, parallel-group trial in New Zealand in adult smokers who were e-cigarette naive and motivated to quit smoking. Participants were recruited from the general population using national media advertising. Participants were randomly assigned (1:4:4), with the use of stratified block randomisation, to receive 14 weeks (2 weeks before the agreed quit date) of 21 mg, 24h nicotine patches, patches plus an 18 mg/L nicotine e-cigarette, or patches plus a nicotine-free e-cigarette. We advised participants to use one patch daily, with e-cigarette use as and when necessary or desired. Participants and researchers were masked to e-liquid nicotine content. We offered 6 weeks of telephone-delivered behavioural support. The primary outcome was exhaled carbon monoxide (CO)-verified continuous smoking abstinence 6 months after the agreed quit date. Primary analysis was by intention to treat, with sensitivity analysis by per protocol, treatment adherence, varying CO cutoffs, and complete case analysis. This paper presents the main analyses and is registered with ClinicalTrials.gov, NCT02521662.

Findings Between March 17, 2016 and Nov 30, 2017, 1124 people were assigned to nicotine patches (patches only group, n=125), patches plus a nicotine e-cigarette (patches plus nicotine e-cigarette group, n=500), or patches plus a nicotine-free e-cigarette (patches plus nicotine-free e-cigarette group, n=499). 62 (50%) of 125 participants in the patches only group withdrew or were lost to follow-up by 6 months compared with 161 (32%) of 500 in the patches plus nicotine e-cigarette group and 162 (33%) of 499 in the patches plus nicotine-free e-cigarette group. 35 (7%) participants in the patches plus nicotine e-cigarette group had CO-verified continuous abstinence at 6 months compared with 20 (4%) in the patches plus nicotine-free e-cigarette group (risk difference [RD] 2·99 [95% CI 0·17–5·81]), and three (2%) people in the patches only group (RD 4·60 [1·11–8·09]). 18 serious adverse events occurred in 16 people in the patches plus nicotine e-cigarette group compared with 27 events in 22 people in the patches plus nicotine-free e-cigarette group and four events in three people in the patches only group. In the patches plus nicotine e-cigarette group, two life-threatening serious adverse events were reported (two separate heart attacks in the one participant). In the patches plus nicotine-free e-cigarette group, one death occurred (accidental drug overdose) and one life-threatening serious adverse event (heart attack). No significant between-group differences were noted for serious adverse events, and none were treatment-related.

Interpretation Combining reduced-harm nicotine products, such as nicotine patches with a nicotine e-cigarette, can lead to a modest improvement in smoking cessation over and above that obtained from using patches plus a nicotine-free e-cigarette (or patches alone), with no indication of any serious harm in the short-term. Future e-cigarette trials should focus on their use alone or in combination with usual smoking cessation support, given issues with differential loss to follow-up and withdrawal if a usual care group is used as a comparator.

Funding Health Research Council of New Zealand.

Lancet Respir Med 2019

Published Online
September 9, 2019
http://dx.doi.org/10.1016/S2213-2600(19)30269-3

See Online/Comment
http://dx.doi.org/10.1016/S2213-2600(19)30308-X

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Introduction

Nicotine replacement therapy (NRT) helps reduce the nicotine withdrawal symptoms experienced by people when they quit smoking. However, no NRT product currently available matches the nicotine concentrations and rapid delivery achieved with smoking. In contrast, contemporary nicotine e-cigarettes enable users to obtain nicotine as rapidly, and potentially in as high concentrations, as that from cigarettes.[1] E-cigarettes, mostly with nicotine, are used by smokers in many countries as an aid to quit smoking.[2] To date, seven clinical trials[3–9] (total N=8222; range n=68 to 6006) have investigated the efficacy and effectiveness of e-cigarettes for smoking cessation and overall suggest a net benefit. However,

Research in context

Evidence before this study

The Cochrane review of e-cigarettes for smoking cessation sought studies published between 2004 and January, 2016. Two trials (N=953) were identified that measured smoking abstinence rates after 6 months or more, and both tested ad libitum use of first-generation e-cigarettes. Combined data from the trials showed that using a nicotine e-cigarette significantly increased smoking abstinence at 6 months compared with using a nicotine-free e-cigarette, although absolute quit rates were low (9% *vs* 4%). No serious adverse events were reported. Confidence in the findings was low given the "small number of trials, low event rates and wide confidence intervals around the estimates". We sought to identify e-cigarette trials that measured smoking abstinence rates at 6 months or more, published between Jan 1, 2016, and June 30, 2019. We searched MEDLINE, Embase, and PsycINFO using the same search terms as the Cochrane Review (e-cig$ OR electr$ cigar$ OR electronic nicotine OR [vape or vaper or vapers or vaping]) plus "Randomized Controlled Trial" (Publication Type). We identified 48 articles, of which two were trials. The first trial (N=54 US companies, 6006 employees and their spouses) tested the effectiveness of four smoking cessation interventions (involving cessation medications, nicotine e-cigarettes, and financial rewards) against usual care (behavioural support). The verified continuous smoking abstinence rate at 6 months in the usual care plus e-cigarette group was higher, but not significantly different, to that observed in the usual care plus cessation medication group (1·0% *vs* 0·5%) or usual care alone (1·0% *vs* 0·1%). The second trial, done within the UK national stop smoking services, tested the effectiveness of second-generation e-cigarettes plus moderate level face-to-face behavioural support for smoking cessation (N=886). Self-reported continuous smoking abstinence rates at 6 months were higher in the 18 mg nicotine e-cigarette group (35·4%) than in those allocated 3 months of nicotine replacement therapy (NRT) (25·1%).

Added value of this study

Our study adds to the scarce trial evidence base on e-cigarettes as a smoking cessation tool and, to our knowledge, is the first to investigate the effectiveness and safety of combining nicotine patches and second-generation e-cigarettes (with and without nicotine) on smoking abstinence. We did the trial in a country with strong tobacco control measures, where advertising is restricted, use of e-cigarettes is low, and there was a ban on the sale of nicotine e-cigarettes. The findings may therefore be generalisable to countries with similar policy backgrounds. For example, Canada, Costa Rica, Ecuador, Japan, and Mexico had similar advertising restrictions on e-cigarettes at the time of the study and Australia, Canada, Costa Rica, Jamaica, Japan, Malaysia, Mexico, and Switzerland prohibited the sale of nicotine e-cigarettes. The research questions addressed in our trial have informed tobacco control policy being developed by the New Zealand Ministry of Health.

Implications of all the available evidence

All five published trials on e-cigarettes for smoking cessation are pragmatic in design, suggesting that under real-world conditions, e-cigarettes (with and without nicotine) could help some people quit smoking but the tobacco control policy environment within which they are available might affect cessation rates. E-cigarettes should be offered as one of the many smoking cessation aids available to people wanting to quit, but do not appear to be a solution for all. People using e-cigarettes should be encouraged to fully switch away from tobacco to e-cigarettes, with the aim of eventually also stopping vaping (if possible) given the lack of any long-term safety data for these devices. Future e-cigarette trials should consider carefully which comparator intervention(s) to use given the high likelihood of differential loss to follow-up (or withdrawal) when only usual care or NRT is offered.

only four trials (N=7849; n=300 to 6006) had 6-month abstinence as a primary outcome[3,4,8,9] and only two trials (total N=6892)[8,9] tested a second-generation e-cigarette (capable of delivering nicotine more effectively than first-generation devices).[10]

In 2015, we did a trial[11] to assess the effectiveness and safety of combining nicotine patches with second-generation e-cigarettes (with and without nicotine liquid [e-liquid]) on smoking abstinence. Moderate intensity behavioural support was available by phone for all participants, given its additional benefit.[12] The trial was done throughout New Zealand, a country with strong tobacco-control policies and an adult smoking prevalence of 16%.[13] When the trial began, it was illegal for nicotine e-liquid to be advertised or sold in New Zealand, but a 3-month supply of nicotine e-liquid could be imported for personal use and nicotine-free e-liquid could be sold. Against this policy background, the prevalence of current e-cigarette use (used at least once a day, week, or month) was low at 3% of adults aged 15 years and older.[14]

The case for maintaining the status-quo for access to nicotine-free e-cigarettes was founded on trial evidence that nicotine-free e-cigarettes help reduce cravings to smoke tobacco and increase quitting in some people;[3,4,15] and if a person wanted to use nicotine, they could use medicinal NRT in addition to nicotine-free e-cigarette use. This argument formed the basis of our primary hypothesis, namely NRT (in this case, patches) plus a nicotine e-cigarette would be more effective at helping smokers quit than patches plus a nicotine-free e-cigarette. Our secondary hypothesis that patches plus a nicotine e-cigarette (combination therapy) would be more effective than patches alone (monotherapy) was based on evidence that combining nicotine patches with faster-acting oral NRT products increases quit rates compared with patches alone.[16]

Methods

Study design and participants

We did a parallel group, community-based, pragmatic, three-arm, randomised trial in New Zealand. The published protocol describes procedures in detail.[11] In brief, people were eligible if they were living in New Zealand, were aged 18 years or older, smoked tobacco (amount not specified), were motivated to quit in the next 2 weeks, were able to provide verbal consent, were prepared to use any of the trial treatments, and had access to a telephone. We excluded pregnant or breastfeeding women, people who had used an e-cigarette for smoking cessation for more than 1 week anytime in the past year, people currently using smoking cessation medication, people enrolled in another cessation programme or study, or who self-reported a history of severe allergies, poorly controlled asthma, or a cardiovascular event in the 2 weeks before enrolment. Only one participant per household was permitted.

We recruited participants using national media advertising and contacted them via text message or phone after registration of interest online. Potential participants were called by a researcher to obtain verbal consent and undertake screening. The Northern A Health and Disability Ethics Committee approved the study (15/NTA/123) and the Standing Committee on Therapeutic Trials approved the use of nicotine e-cigarettes.

Randomisation and masking

The study statistician (VP) prepared the computer-generated randomisation sequence. Eligible participants were randomly allocated by computer to patches, patches plus a nicotine e-cigarette, or patches plus a nicotine-free e-cigarette in a 1:4:4 ratio using stratified block randomisation (block size of nine). An unequal allocation ratio was used in an effort to minimise loss of power from withdrawal or cross-over. Randomisation was stratified by ethnicity: Māori (who comprise 15% of the NZ population[17] and among whom 37% were current smokers in 2015 compared with 16% of the general population)[12] versus non-Māori. Participants and researchers collecting outcome data were masked to the nicotine content of the e-liquid.

Procedures

Moderate-intensity behavioural support was available for all participants immediately after randomisation, then once a week for 6 weeks. This support consisted of 10–15 min of withdrawal-oriented behavioural support[18] and advice on using their allocated treatment, delivered proactively over the phone by researchers who had received standardised training in delivery of such support, including motivational interviewing principles.

Participants received a 14-week supply of their allocated treatment (provided at no cost and couriered in one shipment). A 21 mg, 24 h nicotine patch (Habitrol) was selected because it is the standard patch strength used in New Zealand. The choice of e-cigarette type and brand (plus e-liquid, nicotine strength, and flavours) was informed by our consultation with New Zealand e-cigarette retailers. We selected a second-generation eVOD (Kangertech, Shenzhen GuangDong, China) starter kit, containing two batteries, two refillable tanks, one charging kit, one carry case, and five (2·2 mL, 1·8 OHM) atomisers. Participants had a choice of one of two tobacco e-liquid flavours—one often preferred by those who usually smoke roll-your-own tobacco and one usually preferred by those who smoke factory-made cigarettes. Irrespective of the type of tobacco used by the participant at baseline, they could choose the e-liquid flavour they wanted. The flavours selected for the trial were those recommended by the vaping retailer NZVAPOR (www.nzvapor.com) based on their experience with new e-cigarette users and unpublished sales data. The e-liquid had a 60:40 PG to VG ratio, a masked nicotine content of 0 mg/mL or 18 mg/mL, and was provided in childproof 30 mL brown bottles (four bottles per participant). Independent testing of each batch was done by NicoTar (Roswell Park Cancer Institute, Buffalo, NY, USA). We considered variability of plus or minus 10% nicotine concentration as acceptable. Participants were free to seek out new e-cigarettes and e-liquids if they wished, reflecting the real-world nature of the trial.

We advised participants to start using one patch per day, 2 weeks before their quit-date; although pre-cessation use of NRT is not mentioned as a treatment option in the New Zealand smoking cessation guidelines (unless as part of a cut-down to quit strategy),[19] trial evidence indicates this approach significantly increases long-term quitting success.[20] During this period, participants randomly assigned to an e-cigarette were advised to use the device as and when necessary or desired, and in accordance with the manufacturer's written instructions, to become familiar with its use.[3,21,22] In this way, the time-period of pre-cessation use of treatment products was matched. Written and online video instructions on how to assemble and use an e-cigarette were also provided via a weblink hosted by NZVAPOR, plus participants were advised that they could call NZVAPOR for advice on how to assemble the device, add the e-liquid, and use and maintain the device (reflecting the support offered by the New Zealand vaping community for new e-cigarette users). The above material is available on request from the authors.

Participants were instructed to stop smoking from their quit date and continue with their allocated treatment for 12 weeks (one patch per day, ad libitum use of the e-cigarette), irrespective of any lapses to smoking. 8–12 weeks of NRT treatment is standard care in New Zealand.[19] Participants who had not quit at the end of their time in the trial were referred to publicly funded smoking cessation services. No participant payments were made to encourage retention.

Outcomes

All data (except verification of quit status) were collected by telephone, in calls separate to the behavioural support calls. The published trial protocol[11] presents a tabulated list of outcomes and definitions. In summary, baseline data included date of birth, gender, self-reported ethnicity, years of schooling, self-reported height and weight, smoking history (daily or non-daily smoker, cigarettes smoked per day by daily smokers, age started smoking, years smoked, type of tobacco smoked, quit attempts in the past 12 months and method[s] used), cigarette dependence (measured using the Fagerström Test of Cigarette Dependence, which is on a scale of 1–10, with scores >5 indicating high cigarette dependence and ≤5 indicating low cigarette dependence),[23] concomitant medication, motivation to quit (measured on a 5-point Likert scale, for which 1=very low motivation and 5=very high motivation), tobacco withdrawal symptoms and urge to smoke,[24] urge to vape, household smoking and e-cigarette use, exposure to other e-cigarette users, smoke-free home and car policies, self-reported frequency of shortness of breath and cough (measured on a 5-point Likert scale, for which 1=not at all and 5=all the time), self-reported asthma, chronic obstructive pulmonary disease (COPD), and current and history of mental health problems.

The primary outcome was continuous smoking abstinence 6 months after the agreed quit date (self-reported abstinence since quit date, allowing five or fewer cigarettes in total).[25] Abstinence was verified by a researcher or community-based cessation provider using standardised exhaled carbon monoxide (CO) measurement with a Bedfont Smokerlyzer (Bedfont Scientific Ltd, Kent, UK), with a reading of 9 ppm or lower signifying abstinence.[25] Secondary outcomes assessed at quit date, 1, 3, 6, and 12 months after the agreed quit date were continuous abstinence (CO-verified at 12 months); 7-day point prevalence abstinence (no cigarettes, not a single puff, in the previous 7 days);[25] relapse (time to returning to regular smoking of cigarettes: five cigarettes in the past 7 days); self-reported treatment adherence; tobacco withdrawal symptoms and urge to smoke;[24] urge to vape; self-reported weight; concomitant medication; treatment cross-over; use of other smoking cessation support or medication; continued use of allocated treatment past 14 weeks; changes in shortness of breath, cough, asthma, COPD, and mental health problems; belief in ability to quit and remain tobacco-free; smoking identity (whether those allocated e-cigarettes considered themselves a smoker; a smoker still trying to quit; an ex-smoker; an ex-vapor; a vapor trying to quit smoking; a vapor trying to quit vaping; a vapor, other; or none of the above); and views on their allocated treatment for smoking cessation and whether they would recommend it to other smokers who want to quit. In people still smoking at each follow-up call, outcomes were date returned to daily smoking (for daily smokers); number of cigarettes smoked per day (or when smoking for non-daily smokers); reduction in cigarettes smoked per day; and proportion who reduced the number of cigarettes smoked per day (or when smoking for non-daily smokers) by at least 50%. Participants allocated e-cigarettes were asked about their urge to vape; whether they changed devices or e-liquid, or both; whether they accessed any e-cigarette support or met anyone at least once a week that currently used an e-cigarette; and dual use (daily use of both their allocated e-cigarette and cigarettes).

We recorded prespecified self-reported adverse effects from product use and serious adverse events. Serious adverse events were allocated International Classification of Diseases 10th edition Australian Modification codes and were classified by a physician (CB) as non-serious or serious (death, life-threatening, led to hospitalisation, otherwise medically important [ie, that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the participant or might require medical or surgical intervention to prevent one of the other outcomes]).

Statistical analysis

A sample size of 1809 (804 in both e-cigarette groups and 201 in the patches only group) conferred 90% power, with a two-sided p=0·05 to detect an absolute difference of 8% in 6-month quit rates between the patches plus nicotine e-cigarette group and the patches plus nicotine-free e-cigarette group (1:1 ratio), and a 15% difference between the patches plus nicotine e-cigarette group and the patches only group (4:1 ratio).[11] A 20% loss to follow-up was assumed.[3] The assumed 6-month quit rate of 16% in the patch group was the average observed in the 2012 Cochrane review[16] for nicotine patches versus placebo or no NRT control. The assumed 6-month quit rate of 23% for the patches plus nicotine-free e-cigarette group was based on our trial of NRT combined with very low nicotine cigarettes.[26] The estimated quit rate of 31% for the patches plus nicotine e-cigarette group was observed in a trial comparing patches plus nicotine spray to patches plus placebo spray.[27]

For primary analyses, we used the intention-to-treat (ITT) approach whereby participants with unknown smoking status were deemed to be smoking. The validated primary outcome relates to people who self-reported quitting, could be located, and for whom verification of smoke-free status was confirmed. However, locating people to verify quit status proved difficult given the geographically-dispersed trial population. Therefore, we calculated a post-hoc, extrapolated, validated abstinence rate in which the proportion of people who were located and confirmed as smoke-free was applied to all people who self-reported being smoke-free. We calculated quit rates, relative risks (RR), risk differences (RD), number needed to treat (NNT), and 95% CIs for both comparisons. We compared treatment groups using χ^2 tests. We did adjusted analyses using log-binomial regression and adjusted for the stratification factor (ethnicity).

In prespecified subgroup analyses, we assessed the consistency of effects for the primary outcome for ethnicity, age, sex, education, level of cigarette dependence, motivation to quit, and e-liquid batch using tests for heterogeneity. We did post-hoc subgroup analyses for Māori and non-Māori women. Per-protocol analysis excluded participants with missing 6-month data and major protocol violations. Additional per-protocol analysis also excluded non-adherent participants, with adherence defined as use of both patches and the e-cigarettes (if allocated) at both one and three months. We also did complete case analysis. Sensitivity analyses addressed the effect of varying cutoffs for CO measurements (ie, at ≤3 ppm, ≤5 ppm, and ≤8 ppm).[27] We assessed change from baseline in the number of cigarettes per day (for non-abstainers) and weight and body-mass index over time using repeated measures mixed models with a compound symmetry covariance structure adjusted for baseline value. We used a Mann-Whitney *U* test to compare data that were non-normally distributed. We used Kaplan-Meier curves, the log-rank test, and Cox proportional hazards regression analysis to measure time-to-first-lapse from quit date. We analysed serious adverse events by treatment group, and calculated an incidence rate ratio (IRR) for each comparison. We used SAS (version 9.3) and R for analysis, guided by a prespecified plan. This trial is registered with ClinicalTrials.gov, NCT02521662.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 17, 2016, and Nov 30, 2017, 1623 people were screened, of whom 1124 (69%) were eligible and randomly assigned to the patches only group (n=125), the patches plus nicotine e-cigarette group (n=500), or the patches plus nicotine-free e-cigarette group (n=499; figure). This sample size was less than planned, as the trial ran out of time and funding to continue recruitment due to delays in sourcing nicotine e-liquid and slower than anticipated recruitment.

Last follow-up occurred on Aug 31, 2018. In the patches only group, 42 (34%) of 125 participants were lost to follow-up at 6 months (those with a low level of education and high cigarette dependence were more likely to be lost to follow-up; appendix p 22). In comparison, approximately 30% (152 of 500 and 155 of 499) of participants in each of the two e-cigarette groups were lost to follow-up at 6 months. Participants in the patches plus nicotine e-cigarette group were more likely to be lost to follow-up if they were Māori, were younger than 40 years, or had a low level of education (appendix p 22). Participants in the patches plus nicotine-free e-cigarette group were more likely to be lost to follow-up if they were Māori (appendix p 22).

In the patches only group, 20 (16%) participants withdrew, seven immediately post-randomisation (six citing they did not want to be in the patches only group, and one gave no reason). In comparison, nine (2%) participants withdrew in the patches plus nicotine e-cigarette group, two immediately post-randomisation (one citing they didn't like the products and one providing no reason), and seven (1%) participants withdrew in

See Online for appendix

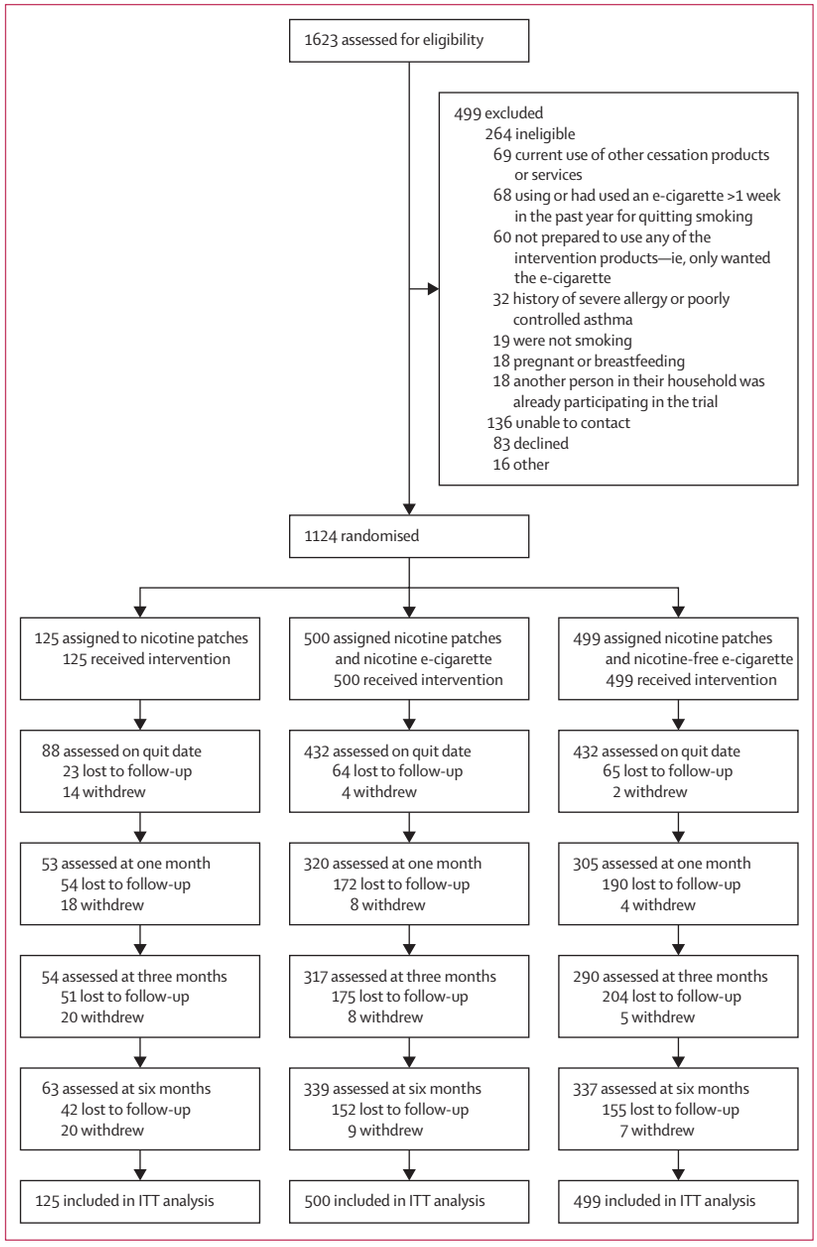

Figure: **Trial profile**
ITT=intention to treat. *People can be in more than one category for exclusion.

	Patches only (n=125)	Patches plus nicotine e-cigarette (n=500)*	Patches plus nicotine-free e-cigarette (n=499)*
Gender			
Women	89 (71%)	329 (66%)	350 (70%)
Men	36 (29%)	170 (34%)	149 (30%)
Gender diverse	0	1 (<1%)	0
Age, years	42·3 (13·1)	41·4 (12·3)	41·2 (12·6)
Ethnicity†			
New Zealand Māori	50 (40%)	202 (40%)	199 (40%)
Non-Māori	75 (60%)	295 (59%)	294 (59%)
Missing	..	3 (1%)	6 (1%)
Education below year 12‡ or no qualification	45 (36%)	179 (36%)	177 (36%)
Smoking status			
Daily smoker	123 (98%)	496 (99%)	492 (99%)
Non-daily smoker	2 (2%)	4 (1%)	7 (1%)
Number of cigarettes (including RYO) smoked per day in daily smokers	17·3 (8·0)	17·3 (8·1)	17·2 (8·7)
Age started smoking, years	15·9 (5·8)	15·3 (4·0)	15·1 (3·8)
Years of smoking	22·4 (12·1)	22·5 (12·3)	22·8 (12·6)
Cigarette dependence§	5·0 (2·1)	5·3 (2·2)	5·2 (2·3)
Type of tobacco usually smoked			
Factory made only	69 (55%)	248 (50%)	246 (49%)
RYO only	34 (27%)	164 (33%)	171 (34%)
Both	22 (18%)	87 (17%)	80 (16%)
Motivated to quit¶	3·8 (0·9)	3·9 (0·9)	3·9 (0·8)
At least one quit attempt in past 12 months	46 (37%)	217 (43%)	244 (49%)
Last method used to quit‖			
Nothing	30 (65%)	108 (50%)	126 (52%)
Nicotine patch	13 (28%)	65 (30%)	69 (28%)
Varenicline	2 (<1%)	26 (12%)	26 (11%)
Nicotine gum	4 (<1%)	20 (9%)	29 (12%)
Nicotine lozenge	3 (<1%)	16 (7%)	19 (8%)
Other**	3 (<1%)	16 (7%)	24 (10%)
Cut down number of cigarettes smoked in the past 12 months	67 (54%)	279 (56%)	288 (58%)
Lives with people who smoke	55 (44%)	214 (43%)	202 (41%)
Lives with people who use-cigarettes	6 (5%)	27 (5%)	34 (7%)
Has close friends who use-cigarettes	57 (46%)	233 (47%)	237 (48%)
Comorbidity (self-reported)			
Current depression†	12 (10%)	67 (13%)	58 (12%)
Current anxiety disorder†	14 (11%)	48 (10%)	49 (10%)
Other current mental illness†	6 (5%)	15 (3%)	20 (4%)
Asthma	15 (12%)	60 (12%)	40 (8%)
COPD	0	14 (3%)	15 (3%)
Frequency of breathing problems (self-reported)††			
Shortness of breath	2·3 (1·1)	2·3 (1·1)	2·3 (1·1)
Cough	2·6 (1·1)	2·5 (1·1)	2·6 (1·1)

Data are mean (SD) or n (%). RYO=roll-your-own (loose tobacco) cigarettes. SD=Standard deviation. COPD=chronic obstructive pulmonary disorder. *The flavours for the patches plus nicotine e-cigarette group were: flavour A (228 [46%]), flavour B (271 [54%]), missing (one [<1%]); the flavours for the patches plus nicotine-free e-cigarette group were: flavour A (222 [45%]), flavour B (276 [55%]), and missing (one [<1%]). †Ethnicity is self-reported. Māori are indigenous New Zealanders. All non-Māori ethnicity categories are aggregated as non-Māori. ‡Age 16 or 17 years. §Cigarette dependence measured using the Fagerström Test of Cigarette Dependence, which is on a scale of 1–10, with scores >5 indicating high cigarette dependence and ≤5 indicating low cigarette dependence. ¶Motivation to quit was measured on a five-point Likert scale, where 1=very low motivation and 5=very high motivation. ‖Multiple choices were possible. **Included Quitline, nicotine mouth spray, bupropion, nortriptyline, cold turkey, doctor, book, food, e-cigarette use for <1 week (unknown if nicotine used), behavioural support via another telephone helpline. ††Frequency measured on a five-point Likert scale, where 1=not at all and 5=all the time.

Table 1: **Baseline characteristics of participants**

the patches plus nicotine-free e-cigarette group, one immediately post-randomisation (citing they had changed their mind).

In March 2018, 4 months after the last person was randomly assigned, and 5 months before the last follow-up call, the New Zealand Ministry of Health allowed nicotine e-cigarettes to be advertised and sold to adult New Zealanders. Before this date, participants could only legally access nicotine e-liquid via the trial or by importing it for personal use. In the patch only group, 19 (15%) of the 125 participants crossed over and used an e-cigarette during the trial (11 [58%] of whom switched within the first 6 weeks of treatment), while 55 (11%) of the 499 participants in the patches plus nicotine-free e-cigarette group crossed over to a nicotine e-cigarette (eight [15%] of whom switched within the first 6 weeks of treatment, but were still included in the ITT analysis).

Baseline characteristics were balanced between the three treatment groups (table 1). Participants were predominantly daily smokers (99%) with a high level of cigarette dependence and motivation to quit. A high proportion of participants were women (768 [68%]; table 1), Māori (451 [40%]), and Māori women (342 [30%]). Overall, 18% of participants reported at least one current mental health problem, 10% reported asthma, and 3% reported COPD (table 1). Additional baseline variables are presented in table 1.

Verified continuous abstinence at 6 months after the agreed quit date was significantly higher in the patches plus nicotine e-cigarette group (35 [7%] of 500) than in the patches plus nicotine-free e-cigarette group (20 [4%] of 499; RR 1·75 [95% CI 1·02–2·98]; p=0·038; RD 2·99 [95% CI 0·17–5·81]; NNT 33·4 [95% CI 17·2–596·1; table 2).

Verified, extrapolated, continuous abstinence rates at 6-months post-quit date were similar to self-reported 6-month continuous abstinence rates. Complete case and per-protocol analyses, and sensitivity analyses around varying CO concentrations, concurred with ITT analysis (table 2). In participants who meet the study definition for treatment adherence, quit rates remained in favour of the patches plus nicotine e-cigarette combination, but did not reach statistical significance (table 2).

In prespecified subgroup analyses we found no significant differences in quit rates nor for post-hoc subgroup analyses comparing quit rates in Māori and

	Patches plus nicotine e-cigarette (n=500)	Patches plus nicotine-free e-cigarette* (n=499)	Relative risk (95% CI)	Risk difference (95% CI)	p value
Continuous abstinence					
Self-reported quit rate at 1 month	189 (38%)	147 (30%)	1·28 (1·08 to 1·53)	8·34 (2·50 to 14·18)	0·005
Self-reported quit rate at 3 months	117 (23%)	69 (14%)	1·69 (1·29 to 2·22)	9·57 (4·78 to 14·36)	<0·001
Self-reported quit rate at 6 months	89 (18%)	53 (11%)	1·68 (1·22 to 2·30)	7·18 (2·87 to 11·49)	0·001
CO-verified quit rate at 6 months (primary outcome)	35 (7%)	20 (4%)	1·75 (1·02 to 2·98)	2·99 (0·17 to 5·81)	0·038
Sensitivity analyses					
Extrapolated adjustment for CO-verification†	85 (17%)	50 (10%)	1·70 (1·22 to 2·35)	6·98 (2·76 to 11·20)	0·001
Complete cases analysis‡	35/330 (11%)	20/328 (6%)	1·74 (1·03 to 2·95)	4·51 (0·30 to 8·72)	0·037
With variable CO cut-offs					
≤3 ppm	31 (6%)	16 (3%)	1·93 (1·07 to 3·49)	2·99 (0·37 to 5·61)	0·026
≤5 ppm	34 (7%)	17 (3%)	2·00 (1·13 to 3·53)	3·39 (0·67 to 6·11)	0·015
≤8 ppm	35 (7%)	20 (4%)	1·75 (1·02 to 2·98)	2·99 (0·17 to 5·81)	0·038
Per protocol§	35/279 (13%)	16/246 (7%)	1·93 (1·10 to 3·40)	6·04 (1·08 to 11·00)	0·020
Treatment adherent¶	12/76 (16%)	7/67 (10%)	1·51 (0·63 to 3·62)	5·34 (–5·65 to 16·33)	0·35
7-day point prevalence abstinence					
Self-reported quit rate at 1 month	198 (40%)	145 (29%)	1·36 (1·14 to 1·62)	10·54 (4·69 to 16·39)	0·001
Self-reported quit rate at 3 months	164 (33%)	116 (23%)	1·41 (1·15 to 1·73)	9·55 (4·01 to 15·09)	0·001
Self-reported quit rate at 6 months	119 (24%)	83 (17%)	1·43 (1·11 to 1·84)	7·17 (2·21 to 12·13)	0·005

Data are n (%) or n/N (%), unless otherwise specified. All data are self-reported and measured post-quit date, unless otherwise specified. All analyses are intention to treat, unless otherwise specified (assumes all participants with missing smoking status were smoking). CO=carbon monoxide. Log-binomial regression analysis adjusted for ethnicity (relative risk 1·85 [95% CI 1·07–3·17]; p=0·027). *55 (11%) people in this group crossed-over to a nicotine e-cigarette: five people self-reported 6-month continuous abstinence from smoking, of which three were CO-verified as abstinent. †Of those who self-reported quitting and were found for a verification test, the number were verified as having quit (this proportion was then extrapolated to the trial population who self-reported quitting). ‡Only includes participants for whom data on smoking status was complete at 6 months. §Excludes participants with missing 6-month data and major protocol violations (death, pregnancy, withdrawals, loss to follow-up at 6 months, cross-over during the 6 month follow-up, randomised in error, randomised to the wrong strata, and not CO-verified). ¶Only those participants who stated they were still using both their patch and e-cigarette (when called at 1 month and 3 months).

Table 2: **Continuous abstinence and 7-day point prevalence abstinence: patches plus nicotine e-cigarette versus patches plus nicotine-free e-cigarette comparison**

	Patches plus nicotine e-cigarette (n=500)	Patches only* (n=125)	Relative risk (95% CI)	Risk difference (95% CI)	p value
Continuous abstinence					
Self-reported quit rate at 1 month	189 (38%)	21 (17%)	2·25 (1·50 to 3·30)	21·0 (13·19 to 28·81)	<0·001
Self-reported quit rate at 3 months	117 (23%)	13 (10%)	2·25 (1·31 to 3·86)	13·00 (6·49 to 19·51)	<0·001
Self-reported quit rate at 6 months	89 (18%)	10 (8%)	2·23 (1·19 to 4·15)	9·80 (3·98 to 15·62)	0·007
CO-verified quit rate at 6 months (primary outcome)	35 (7%)	3 (2%)	2·92 (0·91 to 9·33)	4·60 (1·11 to 8·09)	0·05
Sensitivity analyses					
Extrapolated adjustment for CO-verification†	85 (17%)	9 (7%)	2·36 (1·22 to 4·56)	9·80 (4·20 to 15·40)	0·006
Complete cases analysis‡	35/330 (11%)	3/61 (5%)	2·16 (0·68 to 6·79)	5·69 (-0·67 to 12·05)	0·17
With variable CO cut-offs					
≤3 ppm	31 (6%)	0	..	..	..
≤5 ppm	34 (7%)	3 (2%)	2·83 (0·88 to 9·08)	4·40 (0·93 to 7·87)	0·06
≤8 ppm	35 (7%)	3 (2%)	2·92 (0·91 to 9·33)	4·60 (1·11 to 8·09)	0·05
Per protocol§	35/279 (13%)	3/57 (5%)	2·38 (0·76 to 7·48)	7·28 (0·30 to 14·26)	0·11
7-day point prevalence abstinence					
Self-reported quit rate at 1 month	198 (40%)	22 (18%)	2·25 (1·52 to 3·34)	22·00 (14·07 to 29·93)	<0·001
Self-reported quit rate at 3 months	164 (33%)	21 (17%)	1·95 (1·30 to 2·94)	16·00 (8·26 to 23·74)	0·001
Self-reported quit rate at 6 months	119 (24%)	14 (11%)	2·13 (1·27 to 3·57)	12·60 (5·93 to 19·27)	0·002

Data are n (%) or n/N (%), unless otherwise specified. All data are self-reported and measured post-quit date, unless otherwise specified. All analyses are intention to treat, unless otherwise specified (assumes all participants with missing smoking status were smoking). CO=carbon monoxide. Log-binomial regression analysis adjusted for ethnicity (relative risk 2·90 [95% CI 0·91–9·23]; p=0·027). *19 (15%) people in this group crossed-over to an e-cigarette: only one person self-reported 6-month continuous abstinence from smoking, but this person was not CO-verified as abstinent. †Of those who self-reported quitting and were found for a verification test, how many were verified as having quit (this proportion was then extrapolated to the trial population who self-reported quitting). ‡Only includes participants for whom data on smoking status was complete at 6 months. §Excludes participants with missing 6 month data and major protocol violations (death, pregnancy, withdrawals, loss to follow-up at six months, cross-over during the six month follow-up, randomised in error, randomised to the wrong strata, and not CO verified).

Table 3: **Continuous abstinence and seven-day point prevalence abstinence: patches plus nicotine e-cigarette versus patches only comparison**

non-Māori women (appendix p 9). However, quit rates were significantly higher in the patches plus nicotine e-cigarette group for non-Māori, participants younger than 40 years, non-Māori women, and in those with a low level of cigarette dependence.

Secondary self-reported cessation outcomes at 1, 3, and 6 months after the agreed quit date were consistent with the primary outcome (table 2). In those still smoking, no difference between groups, at any timepoint, was noted for the change from baseline in the mean number of cigarettes smoked per day (appendix p 23). However, a higher proportion in the patches plus nicotine e-cigarette group reduced the number of cigarettes they smoked per day by more than 50% over 3 months compared with people in the patches plus nicotine-free e-cigarette group (54% *vs* 46%; p=0·012; appendix p 23). This difference disappeared by 6 months (44% *vs* 38%; p=0·08; appendix p 23).

We found no significant difference in 6-month verified continuous abstinence rates between the patches plus nicotine e-cigarette group (35 [7%] of 500) and the patches only group (3 [2%] of 125; RR 2·92 [95% CI 0·91–9·33]; p=0·05; RD 4·60 [1·11–8·09]; NNT 21·7 [12·4–90·3]; table 3). Verified, extrapolated, continuous smoking abstinence at 6 months post-quit date was statistically in favour of the patches plus nicotine e-cigarette group (table 3). Complete case and per-protocol analyses found similar findings to the ITT analysis (table 3). However, self-reported secondary cessation outcomes were significantly higher at 1, 3, and 6 months after the agreed quit date in favour of the patches plus nicotine e-cigarette group (table 3). We did not do prespecified subgroup analyses for this comparison due to a small number of participants who quit. In those still smoking, no difference was noted between the two groups at any timepoint for the change from baseline in the mean number of cigarettes smoked per day (appendix p 26). However, the proportion of people reducing the number of cigarettes per day by more than 50% was significantly higher (at all timepoints) in the patches plus nicotine e-cigarette group than in the patches only group (appendix p 26).

Use of the allocated treatments was high at quit date (90% of participants in all three groups reported patch use, 94% reported e-cigarette use, and 85% reported using both products), but decreased over time (table 4). By 3 months, only 50% of participants in all three groups were still using patches, while 67% were still using their nicotine e-cigarette and 56% were still using their nicotine-free e-cigarette (table 4). In the e-cigarette groups, only 33% of participants were still using both of their allocated products at three months. The proportion of participants reporting that they were using their allocated treatment at both

1 month and 3 month follow-up calls was low (23 [56%] of 41 participants in the patches only group, 76 [29%] of 262 participants in the patches plus nicotine e-cigarette group, and 67 [29%] of 229 participants in the patches plus nicotine-free e-cigarette group; table 4), so we did not adjust per-protocol analyses for both primary comparisons for adherence. In those that did use their allocated products in the past 7 days, use was predominantly on a daily basis (appendix pp 10–11). At 6 months after the agreed quit date, 21 (40%) of 52 participants contacted in the patches only group were still using patches (table 4). In comparison, 70 [22%] of 317 participants contacted in the patches plus nicotine e-cigarette group, and 88 [29%] of 308 participants contacted in the patches plus nicotine-free e-cigarette group were still using patches. Furthermore, 143 [45%] of 317 participants contacted in the patches plus nicotine e-cigarette group, and 111 [36%] of 308 participants contacted in the patches plus nicotine-free e-cigarette group were still using their allocated e-cigarette and e-liquid (table 4). The four main reasons given by participants for not using their allocated products during the 3-month treatment period were the same, irrespective of treatment group or product, including they didn't like using them, they hadn't got around to it, unpleasant side-effects, or they felt they didn't need them.

Only a low level of behavioural support was delivered due to difficulties providers faced contacting people: participants received a median of three (IQR 2–5) of the six scheduled support calls (appendix p 12). No between group difference was noted in the level of support delivered for the first comparison; however, participants in the patches plus nicotine e-cigarette group received slightly more calls than those in the patches only group (appendix p 4).

The median time to relapse back to smoking was 5–6 months, with no statistical difference noted for the two comparisons (appendix p 13). Almost 70% of participants allocated to e-cigarettes correctly identified the nicotine content of their e-liquid (appendix p 27). Most participants with asthma, COPD, or mental health problems at baseline reported that their condition remained the same or improved over time (appendix p 5). The prevalence of self-reported side-effects of treatment was low (appendix p 28). Data for other secondary and post-hoc outcomes can be found in the appendix (pp 1–32).

18 serious adverse events occurred in 16 people in the patches plus nicotine e-cigarette group compared with 27 events in 22 people in the patches plus nicotine-free e-cigarette group (IRR 0·66 [95% CI 0·36–1·20]; p=0·18), and four events in three people in the patches only group (0·86 [0·29–2·53]; p=0·78; table 5; appendix p 24–25). No serious adverse events were treatment related.

	Patches only	Patches plus nicotine e-cigarette	Patches plus nicotine-free e-cigarette
Quit date*	N=87	N=428	N=432
Patches only	79 (90%)	383 (90%)	386 (89%)
E-cigarette only	..	401 (94%)	408 (94%)
Both patch and e-cigarette	..	364 (85%)	370 (86%)
1 month*	N=53	N=320	N=304
Patches only	43 (81%)	220 (69%)	224 (74%)
E-cigarette only	..	260 (81%)	257 (85%)
Both patch and e-cigarette	..	187 (58%)	199 (66%)
3 months*	N=54	N=317	N=289
Patches only	26 (48%)	146 (46%)	144 (50%)
E-cigarette only	..	212 (67%)	162 (56%)
Both patch and e-cigarette	..	105 (33%)	94 (33%)
Use at both 1 month and 3 months*	N=41	N=262	N=229
Patches only	23 (56%)	109 (42%)	105 (26%)
E-cigarette only	..	166 (63%)	121 (53%)
Both patch and e-cigarette	..	76 (29%)	67 (29%)
6 months*	N=52	N=317	N=308
Patches only	21 (40%)	70 (22%)	88 (29%)
E-cigarette only	..	143 (45%)	111 (36%)
Both patch and e-cigarette	..	36 (11%)	41 (13%)

Data are n (%). *Adherence was defined as having used the allocated product since last contacted (frequency of use not defined). Findings relate to allocated treatment only, in participants for whom adherence data were available. Data does not include adherence in those who crossed-over to an e-cigarette or those who changed their type of e-cigarette.

Table 4: **Adherence with allocated treatment during 12-week intervention period and at 6 months follow-up**

	Patches only (n=125)	Patches plus nicotine e-cigarette (n=500)	Patches plus nicotine-free e-cigarette (n=499)
Participants with a serious adverse event	4 (3%)	18 (4%)	27 (5%)
Serious adverse events*			
Death†	0	0	1
Life-threatening‡	0	2	1
Hospitalisation	3	11	19
Persistent, significant disability, or incapacity	0	1	0
Otherwise medically important	1	4	6

Data are n (%). *Categories are mutually exclusive. †One death occurred in the patches plus nicotine-free e-cigarette group (accidental drug overdose). ‡In the patches plus nicotine e-cigarette group, one person had two separate heart attacks; in the patches plus nicotine-free e-cigarette group, one person had a heart attack.

Table 5: **Summary of all-cause serious adverse events**

Discussion

This effectiveness trial found that a combination of nicotine patches plus a nicotine e-cigarette was superior to patches plus a nicotine-free e-cigarette for 6 month smoking abstinence among dependent smokers motivated to quit. For the patches plus nicotine e-cigarette versus patches plus nicotine-free e-cigarette comparison, as well as for the patches plus nicotine e-cigarette versus patches only comparison, self-reported, self-reported quit rates at all timepoints were in favour of patches plus a nicotine e-cigarette, so the fact that the comparison of patches plus a nicotine e-cigarette versus patches alone did not reach significance is likely to be a result of the smaller than anticipated sample size. Overall, the

observed absolute 6-month quit rates in the e-cigarette groups were low and similar to rates reported in the first trials[28] of e-cigarettes for smoking cessation that used first-generation devices with minimal behavioural support.[3,4] However, quit rates at 1 months and 3 months in the e-cigarette groups in the current study were almost twice those reported in two early trials.[3,4] The safety findings are consistent with previous e-cigarette trials and cohort study findings.[9,29] Despite a higher proportion of participants in the patches only group using the patch (compared with patch use in the other treatment groups), 6-month self-reported and verified absolute quit rates for this group were low, but similar to those observed in trials of over-the-counter NRT.[30]

Our study is the second largest e-cigarette trial to date with a primary outcome of at least 6-month smoking abstinence. To our knowledge, it is also the first large trial testing the effectiveness of a second-generation e-cigarette for smoking cessation within the general population and with the selection of e-cigarette and e-liquid based on advice from vaping retailers. Two previous trials also tested a second-generation e-cigarette.[8,9] One five-arm trial[8] was web-based (undertaken in the USA in company employees and their partners), with only 1191 (19·8%) of 6006 randomly assigned participants logging onto the website to access the interventions, and only 467 (8%) accessing e-cigarettes. Compared with our trial, the verified continuous smoking abstinence rate at 6 months in the USA trial[8] was low for those allocated behavioural support combined with access to free nicotine e-cigarettes (12 [1·0%] of 1199). In contrast, the second trial[9] was set within a UK national smoking cessation service (with moderate intensity face-to-face behavioural support) and reported much higher self-reported 6-month continuous abstinence rates than observed in our trial (35% in the nicotine e-cigarette group and 25% in the NRT group). Since all three trials commenced, newer e-cigarette products have emerged that can deliver nicotine more effectively than the trial devices,[31] but the cessation effectiveness and safety of these new devices have yet to be assessed.

One of the strengths of our trial was its pragmatic design, with broad entry criteria and no payment to improve medication adherence and retention. Therefore, the generalisability of our findings to the real world is high, particularly in countries with strong tobacco control measures and low promotion and uptake of e-cigarettes. The high enrolment by indigenous Māori (especially Māori women) and people with current mental health problems suggests high levels of motivation to try new ways of quitting in these populations with a high smoking prevalence. The internal validity of the trial was also high: we controlled for selection bias by undertaking computer randomisation and stratification a priori by ethnicity. No baseline imbalances were noted. We ensured allocation concealment because the statistician who generated the random allocation was not the person randomising participants. Given the decline in treatment use by many participants over 3 months, performance bias could be an issue. However, we advised all participants to use their allocated patch once per day and their e-cigarette as and when necessary or desired, reflecting recommended use of both products. In this real-world scenario, use of patches and e-cigarettes is not sustained by most people trying to quit, with e-cigarettes more commonly used than patches. However, some people continued to use patches or e-cigarettes, or both, long-term. The trial results therefore more accurately reflect the true effect of these behaviours on smoking abstinence rates. Our use of ITT analysis gave a conservative treatment effect.

We acknowledge several limitations of our study. First, our inability to reach the recruitment target restricted the ability to do some comparisons. Second, loss to follow-up was 10% higher than anticipated and there were systematic differences in the number of participants who were non-contactable (suggesting our findings might not be as generalisable to Māori, people younger than 40 years, and people with a lower level of education who are trying to quit smoking) or who withdrew (ie, more people withdrew in the patches only group, particularly immediately after randomisation). Given these biases, greater weight should be placed on the findings of the per-protocol analysis for both comparisons (although they produced similar and consistent results to the ITT analysis, suggesting our findings are robust). Although participants were willing to be randomly assigned to any of the three groups, withdrawal and cross-over in those not allocated a nicotine e-cigarette highlights the greater appeal a nicotine e-cigarette had compared with nicotine patches (which 30% of participants had used to support their last quit attempt, with no success). Third, while we attempted to minimise detection bias by masking the nicotine content of the e-liquid, we were only 30% successful, and thus some bias in favour of nicotine e-cigarettes could have occurred. Fourth, we considered but did not include a fourth group (placebo patches plus a nicotine e-cigarette) because to do so would have exceeded the available funding. Besides, our earlier trial[3] examined the effectiveness of nicotine e-cigarettes versus patches for smoking cessation. Fifth, participants in the patches plus nicotine e-cigarette group received slightly more behavioural support calls than the patches only group, which might have increased the likelihood of quitting success. Sixth, the use of patches differed to what participants might have been used to in the past, in that we started product use 2 weeks before the target quit date. This change did not affect adherence (because product use at quit date was very high), but might limit the generalisable of the findings to policy environments where precessation use of NRT is not supported. Finally, serious adverse events were self-reported and similar to

those reported in previous e-cigarette[3–7,9] and NRT trials.[16] However, the sample size was not sufficient to assess uncommon serious adverse events, nor was follow-up long enough to identify serious adverse events with a long lead-time.

In summary, when looking at continuous abstinence from smoking, provision of patches plus a nicotine e-cigarette resulted in three to seven more smokers per 100 quitting long-term (depending on the analyses done) than with patches plus a nicotine-free e-cigarette. The smaller than anticipated sample size meant the study was not sensitive enough to pick up a definitive finding for the second comparison, although analyses suggest combination nicotine therapy—ie, use of a slow release nicotine patch, together with a faster-acting oral nicotine product (in this case a nicotine e-cigarette)—could result in five to ten more smokers per 100 quitting long-term than with monotherapy (ie, nicotine patches alone). Our findings are consistent with the current findings of the Cochrane review of e-cigarettes for smoking cessation[29] and contribute to the growing body of evidence from randomised trials on the efficacy, effectiveness and safety of e-cigarettes for smoking cessation.

Contributors

NW, VP, GL, ML, and CB conceived the original idea for the trial, and sought and obtained funding. All authors contributed to the writing of the study protocol. VP did all data analyses. The paper was written by NW, with input from all co-authors. NW is guarantor for this paper. All authors read and approved the final manuscript.

Declaration of interests

NW, CB, MV, GL, ML, and VP report grants from the Health Research Council of New Zealand, during the conduct of the study. NW, CB, MV, and VP report grants from Pfizer, outside of the submitted work. GL chairs the organisation End Smoking New Zealand, which advocates for harm reduction approaches to tobacco control. E-cigarettes were purchased from a New Zealand e-cigarette online retailer (NZVAPOR, https://www.nzvapor.com/), e-liquid was purchased from Nicopharm, Australia (https://www.nicopharm.com.au/), and nicotine patches were supplied by the New Zealand Government via their contract with Novartis (Sydney, Australia). NZVAPOR also provided, at no cost to participants, on-line and phone support regarding use of the e-cigarettes. Neither NZVAPOR nor Nicopharm have links with the tobacco industry. None of the above parties had any role in the design, conduct, analysis, or interpretation of the trial findings, or writing of this publication.

Data sharing

Requests for de-identified individual participant data or study documents will be considered where the proposed use aligns with public good purposes, does not conflict with other requests or planned use by the trial steering committee, and the requestor is willing to sign a data access agreement. Contact is through the corresponding author.

Acknowledgments

We thank the Health Research Council of New Zealand, NZVAPOR, Nicopharm, trial participants, community-based smoking cessation providers from throughout New Zealand, and the many study-related staff at the National Institute for Health Innovation who contributed to the conduct of this trial. The following organisations offered support with recruitment by promoting our trial via their websites and social media channels: The University of Auckland, Auckland UniServices, NZVAPOR, Homecare Medical (Quitline), Cancer Society New Zealand, Breast Cancer Society New Zealand, Heart Foundation, Green Cross, Hāpai Te Hauora, and Hauora Tairawhiti.

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