

Electronic cigarettes for smoking cessation: a randomised controlled trial



Christopher Bullen, Colin Howe, Murray Laugesen, Hayden McRobbie, Varsha Parag, Jonathan Williman, Natalie Walker

Summary

Background Electronic cigarettes (e-cigarettes) can deliver nicotine and mitigate tobacco withdrawal and are used by many smokers to assist quit attempts. We investigated whether e-cigarettes are more effective than nicotine patches at helping smokers to quit.

Methods We did this pragmatic randomised-controlled superiority trial in Auckland, New Zealand, between Sept 6, 2011, and July 5, 2013. Adult (≥ 18 years) smokers wanting to quit were randomised (with computerised block randomisation, block size nine, stratified by ethnicity [Māori; Pacific; or non-Māori, non-Pacific], sex [men or women], and level of nicotine dependence [>5 or ≤ 5 Fagerström test for nicotine dependence]) in a 4:4:1 ratio to 16 mg nicotine e-cigarettes, nicotine patches (21 mg patch, one daily), or placebo e-cigarettes (no nicotine), from 1 week before until 12 weeks after quit day, with low intensity behavioural support via voluntary telephone counselling. The primary outcome was biochemically verified continuous abstinence at 6 months (exhaled breath carbon monoxide measurement <10 ppm). Primary analysis was by intention to treat. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000866000.

Findings 657 people were randomised (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) and were included in the intention-to-treat analysis. At 6 months, verified abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with patches, and 4.1% (three of 73) with placebo e-cigarettes (risk difference for nicotine e-cigarette vs patches 1.51 [95% CI -2.49 to 5.51]; for nicotine e-cigarettes vs placebo e-cigarettes 3.16 [95% CI -2.29 to 8.61]). Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. We identified no significant differences in adverse events, with 137 events in the nicotine e-cigarettes group, 119 events in the patches group, and 36 events in the placebo e-cigarettes group. We noted no evidence of an association between adverse events and study product.

Interpretation E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events. Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels.

Funding Health Research Council of New Zealand.

Introduction

Since their launch in 2004, electronic cigarettes (e-cigarettes), a diverse range of battery operated devices that vaporise nicotine for inhalation, have been purchased by millions of people.¹ Many smokers use e-cigarettes to help them quit (27% of those making a quit attempt in the UK, in May, 2013²), and sales are increasing so rapidly that some analysts predict that they will surpass cigarette sales within a decade.¹

The place of e-cigarettes in tobacco control is controversial,^{3,4} and there is a paucity of reliable data to inform debate. Available research suggests that e-cigarettes have the potential to assist smokers to quit or reduce smoking: surveys show that many smokers try e-cigarettes for these reasons,^{5,6} and studies show that e-cigarettes are capable of delivering nicotine into the bloodstream and attenuating tobacco withdrawal as effectively as nicotine replacement therapy (NRT).^{7,8} Use of e-cigarettes also simulates behavioural and sensory

dimensions of smoking. However, a trial in 300 smokers unwilling to quit showed low rates of cessation at 12 months for nicotine e-cigarettes and placebo e-cigarettes.⁹ E-cigarettes also have potential to harm: researchers have detected toxins in e-cigarette fluid and vapour,¹⁰ but at much the same concentrations as with NRT and lower than in cigarette smoke;¹¹ a review deemed e-cigarettes to be very unlikely to pose significant risks to smokers.¹²

In this trial we aimed to assess whether e-cigarettes with cartridges containing nicotine (nicotine e-cigarette) were more effective for smoking cessation than nicotine patches, and included a blind comparison with e-cigarettes containing no nicotine (placebo e-cigarette). We hypothesised that nicotine e-cigarettes would be more effective than patches and placebo e-cigarettes for smoking reduction, tobacco dependence, and relief of withdrawal symptoms, and that they would have no greater risk of adverse events than nicotine patches.

Lancet 2013; 382: 1629–37

Published Online
September 7, 2013
[http://dx.doi.org/10.1016/S0140-6736\(13\)61842-5](http://dx.doi.org/10.1016/S0140-6736(13)61842-5)

See [Comment](#) page 1614

National Institute for Health Innovation, School of Population Health, The University of Auckland, Auckland, New Zealand (C Bullen MBChB, C Howe PhD, V Parag MSc, N Walker PhD); Health New Zealand, Lyttelton, Christchurch, New Zealand (M Laugesen MBChB); Wolfson Institute of Preventive Medicine, UK Centre for Tobacco Control Studies, Queen Mary University of London, Charterhouse Square, London, UK (H McRobbie MBChB); and Department of Public Health and General Practice, University of Otago, Christchurch, New Zealand (J Williman PhD)

Correspondence to:
Dr Christopher Bullen, The National Institute for Health Innovation, School of Population Health, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
c.bullen@nihi.auckland.ac.nz

Methods

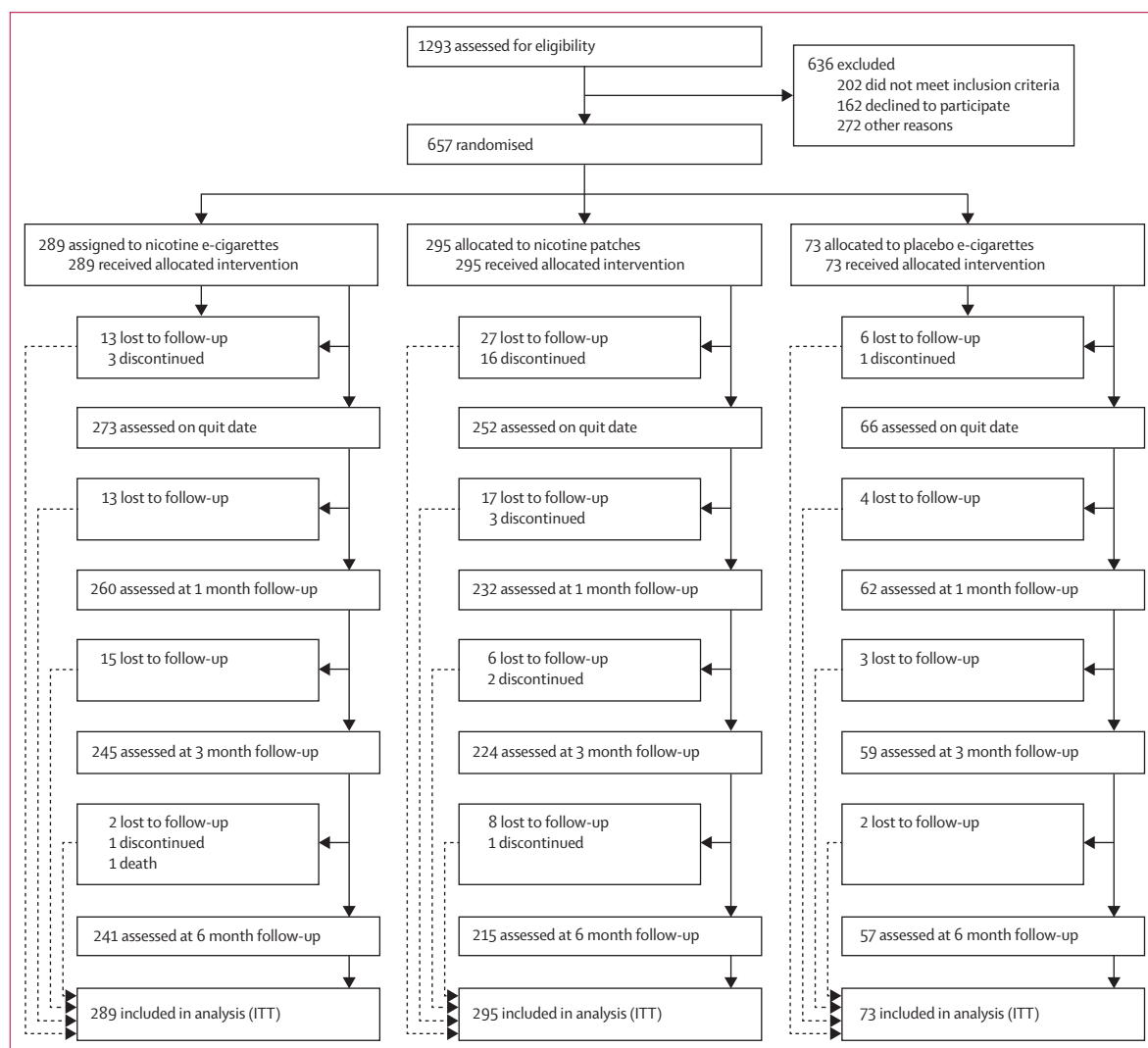
Study design and participants

We did this three parallel group, randomised controlled trial in Auckland, New Zealand. First randomisation was on Sept 6, 2011, and last follow-up was on July 5, 2013. The published protocol describes procedures in detail.¹³ In brief, people were eligible if they were aged 18 years or older, had smoked ten or more cigarettes per day for the past year, wanted to stop smoking, and could provide consent. We recruited via community newspapers, inviting people to call the study centre for eligibility prescreening, done by research assistants, who also completed follow-up assessments. We excluded pregnant and breastfeeding women; people using cessation drugs or in an existing cessation programme; those reporting heart attack, stroke, or severe angina in the previous

2 weeks; and those with poorly controlled medical disorders, allergies, or other chemical dependence. Participants were mailed study information, and consent forms to sign and return. The Northern X Regional Ethics Committee approved the study (Number NTX/10/11/111); the Standing Committee on Therapeutic Trials approved the use of nicotine e-cigarettes because they were not permitted for sale in New Zealand, but could be imported for personal use or research.

Randomisation and masking

Callers who met the inclusion criteria and gave demographic details and information about nicotine dependence (Fagerström test for nicotine dependence [FTND]¹⁴) were randomised by the study statistician (VP) in a 4:4:1 ratio to nicotine e-cigarettes, patches, or placebo



e-cigarettes, with computerised block randomisation, block size nine, stratified by: ethnicity (Māori; Pacific; or non-Māori, non-Pacific), sex (men or women), and level of nicotine dependence (>5 or ≤ 5 FTND). It was not feasible to mask participants to allocation to patch or e-cigarettes. Research assistants undertaking outcome assessments used a list generated by the trial database giving no indication of product allocation.

Procedures

Elusion e-cigarettes are among the e-cigarette market leaders in Australasia; in New Zealand, nicotine e-cigarettes are not permitted to be sold, but nicotine-free e-cigarettes are widely available for sale and identical in appearance to nicotine versions. We commissioned analyses of these e-cigarettes: the liquid was free of diethylene glycol (a toxin detected in fluid in one brand of e-cigarettes¹⁰); nicotine cartridges (labelled 16 mg) contained 10–16 mg nicotine per mL; and placebo cartridges contained no nicotine. Vapour analyses done midway through the trial (using Goniewicz and colleagues' methodology¹⁵) showed that 300 puffs from one nicotine e-cigarette cartridge delivered 3–6 mg nicotine, equivalent to smoking between one and five tobacco cigarettes. The first 20 participants randomised to the nicotine e-cigarettes group were invited to take part in testing, and four completed the testing regimen. In these four participants, who had been using the nicotine e-cigarettes for at least 1 week, plasma nicotine concentrations were sampled every 10 min for 1 h, and peaked at 10 min after commencement of product use at 3.4 ng/mL, a median increase from baseline of 2.1 ng/mL. We chose nicotine patches (21 mg/24 h) for comparison with e-cigarettes because they are the most popular NRT product in New Zealand,¹⁶ have proven effectiveness,¹⁷ and few known adverse events.¹⁷

Participants allocated to patches were sent exchange cards in the mail redeemable for patches from community pharmacies, with instructions to use patches daily, from 1 week before until 12 weeks after their chosen quit day, consistent with smoking cessation guidelines.¹⁸ We also supplied vouchers to these participants to cover dispensing costs. Participants in both e-cigarettes groups were couriered an e-cigarette, spare battery and charger, and cartridges (with labels masked to nicotine content), plus simple instructions to use them as desired from 1 week before until 12 weeks after their chosen quit day. All randomised participants were referred (by fax or by a scanned request) to Quitline, who called the participants to offer telephone-based behavioural support. Participants who declined or did not call back were still able to access other Quitline support, such as Txt2Quit (a free SMS support service). Quitline provided us with reports to monitor usage. After randomisation, additional baseline data were collected: education, smoking and quitting history, quitting self-efficacy, medication, withdrawal symptoms and stage of addiction (according to the autonomy over smoking scale, AUTOS),¹⁹ and behavioural

dependence (according to the Glover-Nilsson smoking behavioural questionnaire, GN-SBQ).²⁰

The primary outcome was continuous smoking abstinence (self-reported abstinence over the whole follow-up period, allowing ≤ 5 cigarettes in total²¹), 6 months after quit day, verified at that point in time by exhaled breath carbon monoxide measurement (<10 ppm), using Bedfont Micro Smokerlyzers (Bedfont Scientific, Maidstone, UK). Carbon monoxide tests were administered by research assistants at the University of Auckland; participants were not paid for testing, but received transportation costs. Secondary outcomes assessed at 1, 3, and 6 months post quit day were: continuous abstinence, 7 day point prevalence abstinence (proportion reporting no smoking of tobacco cigarettes, not a puff, in the past 7 days), number of tobacco cigarettes smoked per day, proportion of participants reducing tobacco smoking, time to relapse to tobacco smoking, number of patches or cartridges used, use of other cessation treatments, withdrawal symptoms, stage of addiction,¹⁹ smoking latency,²² and adverse events. Data collection continued as scheduled if participants discontinued study treatments.

Statistical analysis

A sample size of 657 (292 in the nicotine e-cigarettes group, 292 in the patches group, 73 in the placebo

| | Nicotine e-cigarettes (n=289) | Patches (n=295) | Placebo e-cigarettes (n=73) |
|---|-------------------------------------|--------------------|-----------------------------------|
| Age (years) | 43.6 (12.7) | 40.4 (13.0) | 43.2 (12.4) |
| Women | 178 (62%) | 182 (62%) | 45 (62%) |
| Ethnicity* | | | |
| New Zealand Māori | 95 (33%) | 95 (32%) | 23 (32%) |
| Non-Māori | 194 (67%) | 200 (68%) | 50 (68%) |
| Education below year 12† or no qualification | 150 (52%) | 123 (42%) | 38 (52%) |
| Average number of cigarettes (including RYO) smoked per day | 18.4 (7.2) | 17.6 (6.0) | 17.7 (5.6) |
| Age started smoking (years) | 15.6 (4.7) | 15.2 (3.8) | 15.7 (5.1) |
| Number of years smoking continuously | 25.9 (13.1) | 23.5 (12.9) | 24.8 (13.7) |
| Type of tobacco usually smoked | | | |
| Factory made only | 167 (58%) | 167 (57%) | 47 (64%) |
| RYO only | 92 (32%) | 92 (31%) | 21 (29%) |
| Both | 30 (10%) | 35 (12%) | 5 (7%) |
| Lives with other smokers | 151 (52%) | 149 (51%) | 42 (58%) |
| At least 1 quit attempt in past 12 months | 158 (55%) | 169 (57%) | 39 (53%) |
| FTND score | 5.6 (2.0) | 5.5 (2.0) | 5.5 (2.0) |
| FTND >5 (high dependence) | 157 (54%) | 162 (55%) | 40 (55%) |
| GN-SBQ score | 20.1 (7.9) | 20.1 (8.4) | 21.4 (8.6) |
| Self-efficacy to quit‡ | 3.7 (1.0) | 3.7 (0.9) | 3.6 (1.0) |
| AUTOS total score | 22.6 (7.2) | 23.1 (7.6) | 23.4 (7.3) |

Data are mean (SD) or n (%). RYO=roll your own (loose tobacco) cigarettes. FTND=Fagerström test of nicotine dependence. GN-SBQ: Glover-Nilsson smoking behavioural questionnaire. AUTOS=autonomy over smoking scale; higher scores indicate greater dependence. *All non-Māori ethnicity categories aggregated as non-Māori.²³ †Age 16 or 17 years. ‡Self-efficacy to quit=belief in ability to quit this time, measured on scale of 1 to 5, 1=very low, 5=very high.

Table 1: Baseline characteristics of participants

| | Nicotine e-cigarettes (n=289) | Patches (n=295) | Difference χ^2 p value | Relative risk (95% CI) | Risk difference (95% CI) |
|---|-------------------------------|-----------------|-----------------------------|------------------------|--------------------------|
| Continuous abstinence | | | | | |
| 1 month | 67 (23.2%) | 47 (15.9%) | 0.03 | 1.46 (1.04 to 2.04) | 7.25 (0.84 to 13.66) |
| 3 months | 38 (13.1%) | 27 (9.2%) | 0.12 | 1.44 (0.90 to 2.33) | 4.00 (-1.10 to 9.10) |
| 6 months (primary outcome) | 21 (7.3%) | 17 (5.8%) | 0.46 | 1.26 (0.68 to 2.34) | 1.51 (-2.49 to 5.51) |
| Sensitivity analyses for 6 months continuous abstinence data | | | | | |
| Complete case analysis* | 21/241 (8.7%) | 17/215 (7.9%) | 0.76 | 1.10 (0.60 to 2.03) | 0.80 (-4.27 to 5.87) |
| Per-protocol analysis 1† | 21/231 (9.1%) | 15/207 (7.2%) | 0.48 | 1.25 (0.66 to 2.37) | 1.84 (-3.28 to 6.96) |
| Per-protocol analysis 2‡ | 20/211 (9.5%) | 13/151 (8.6%) | 0.78 | 1.10 (0.57 to 2.14) | 0.87 (-5.10 to 6.84) |
| Per-protocol analysis 3§ | 12/147 (8.2%) | 12/138 (8.7%) | 0.87 | 0.94 (0.44 to 2.02) | -0.54 (-7.00 to 5.92) |
| Including not biochemically verified¶ | 30 (10.4%) | 21 (7.1%) | 0.16 | 1.46 (0.86 to 2.49) | 3.26 (-1.32 to 7.84) |
| Repeated measures analysis | | | | | |
| Overall treatment effect | .. | .. | 0.05 | 1.61 (1.00 to 2.57) | .. |
| 1 month effect | .. | .. | 0.004 | 1.87 (1.23 to 2.85) | .. |
| 3 months effect | .. | .. | 0.12 | 1.52 (0.89 to 2.58) | .. |
| 6 months effect | .. | .. | 0.21 | 1.46 (0.81 to 2.62) | .. |
| 7 day point prevalence abstinence | | | | | |
| 1 month | 69 (23.9%) | 51 (17.3%) | 0.05 | 1.38 (1.00 to 1.91) | 6.59 (0.05 to 13.13) |
| 3 months | 62 (21.5%) | 50 (17.0%) | 0.17 | 1.27 (0.91 to 1.77) | 4.50 (-1.88 to 10.88) |
| 6 months | 61 (21.1%) | 46 (15.6%) | 0.09 | 1.35 (0.96 to 1.91) | 5.52 (-0.75 to 11.79) |

All analyses are intention to treat unless otherwise specified (assumes participants with missing smoking status were smoking). Data are n (%) or n/N (%) unless otherwise specified. *Complete case analysis: excludes 128 participants with missing 6 month visits (withdrawn or lost to follow-up; 48 in nicotine e-cigarettes group and 80 in patches group), and includes 456 participants (241 in nicotine e-cigarettes group and 215 in patches group). †Per-protocol analysis 1: excludes protocol violations: pregnancy, death, quitters who did not have biochemical verification, undisclosed medication ineligibility, withdrew, and lost to follow-up at 6 months. ‡Per-protocol analysis 2: excludes protocol violations from per-protocol analysis 1 plus: cross-overs, use of other or combined nicotine replacement therapy products, and use of non-nicotine replacement therapy (eg, varenicline). §Per-protocol analysis 3: excludes protocol violations from per-protocol analysis 2 plus: participants still using product to which they were randomised at 6 months. ¶Continuous abstinence including not biochemically verified: eight participants in nicotine e-cigarettes group: one moved, two refused, four did not attend appointment, one adverse event (birth) did not want to attend; four participants in patches group: one moved, three refused. ||Output for repeated measures analysis is difference in least squares means, not relative risk.

Table 2: Continuous smoking abstinence and 7 day point prevalence, nicotine e-cigarettes versus patches

e-cigarettes group) conferred 80% power, with two-sided $p=0.05$, to detect an absolute difference of 10% in quit rates between the nicotine e-cigarettes group and patches group (1:1 ratio), and a 15% difference between the nicotine e-cigarettes group and placebo e-cigarettes group (4:1 ratio), with expected quit rates of 15% in the placebo e-cigarettes group and 20% in the patches group (based on meta-analyses of NRT trials).²³ We used SAS (version 9.3) for analyses. The primary analyses used the intention-to-treat approach (participants with unknown smoking status were assumed to be smoking). We calculated quit rates, relative risks (RR), and absolute risks for nicotine e-cigarettes versus patches, and for nicotine e-cigarettes versus placebo e-cigarettes. We compared treatment groups using χ^2 tests, with multivariate regression adjusting for other variables as appropriate. The proportions of participants with significantly reduced smoking consumption of at least 25% and 50% were calculated using the same methods. Change from baseline in each of the repeated AUTOS measures and cigarettes smoked per day (in non-abstainers) were analysed using mixed models with a compound symmetry covariance structure

including baseline values. We also did per-protocol analyses for the primary outcome, in which participants with major protocol violations (eg, cross-over treatments, withdrawals, and loss to follow-up) were excluded. We assessed consistency of effects for pre-specified subgroups (men vs women, ethnicity [Māori vs non-Māori]) using tests for heterogeneity. Secondary analyses were done with overall cessation rates corrected for discordance between reported and verified cessation. We used Kaplan-Meier curves and the log-rank test for analyses of time to relapse. Adverse events were defined according to international guidelines, categorised by CB (masked to intervention product) as related or unrelated to the intervention, and analysed as serious or non-serious, by treatment group and association with study treatment, in line with recommended best practice.²⁴

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12610000866000.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or

| | Nicotine e-cigarettes (n=289) | Placebo e-cigarettes (n=73) | Difference Fisher's exact p value | Relative risk (95% CI) | Risk difference (95% CI) |
|---|----------------------------------|--------------------------------|--------------------------------------|---------------------------|-----------------------------|
| Continuous abstinence | | | | | |
| 1 month* | 67 (23.2%) | 12 (16.4%) | 0.21 | 1.41 (0.81 to 2.46) | 6.74 (-3.06 to 16.54) |
| 3 months* | 38 (13.1%) | 5 (6.8%) | 0.14 | 1.92 (0.78 to 4.70) | 6.30 (-0.68 to 13.28) |
| 6 months (primary outcome) | 21 (7.3%) | 3 (4.1%) | 0.44 | 1.77 (0.54 to 5.77) | 3.16 (-2.29 to 8.61) |
| Sensitivity analyses for 6 months continuous abstinence data | | | | | |
| Complete case analysis† | 21/241 (8.7%) | 3/57 (5.3%) | 0.59 | 1.66 (0.51 to 5.36) | 3.45 (-3.35 to 10.25) |
| Per-protocol analysis 1‡ | 21/231 (9.1%) | 3/54 (5.6%) | 0.59 | 1.64 (0.51 to 5.29) | 3.53 (-3.62 to 10.68) |
| Per-protocol analysis 2§ | 20/211 (9.5%) | 2/46 (4.3%) | 0.36 | 2.18 (0.53 to 9.00) | 5.13 (-1.97 to 12.23) |
| Per-protocol analysis 3¶ | 12/147 (8.2%) | 1/30 (3.3%) | 0.70 | 2.45 (0.33 to 18.13) | 4.83 (-2.97 to 12.63) |
| Including not biochemically verified | 30 (10.4%) | 4 (5.5%) | 0.26 | 1.89 (0.69 to 5.21) | 4.90 (-1.39 to 11.20) |
| Repeated measures analysis** | | | | | |
| Overall treatment effect | .. | .. | 0.13 | 1.91 (0.83 to 4.37) | .. |
| 1 month effect | .. | .. | 0.09 | 1.80 (0.90 to 3.61) | .. |
| 3 months effect | .. | .. | 0.16 | 2.00 (0.76 to 5.28) | .. |
| 6 months effect | .. | .. | 0.23 | 1.92 (0.65 to 5.66) | .. |
| 7 day point prevalence abstinence | | | | | |
| 1 month* | 69 (23.9%) | 12 (16.4%) | 0.17 | 1.45 (0.83 to 2.53) | 7.44 (-2.38 to 17.26) |
| 3 months* | 62 (21.5%) | 12 (16.4%) | 0.34 | 1.31 (0.74 to 2.29) | 5.01 (-4.72 to 14.74) |
| 6 months* | 61 (21.1%) | 16 (21.9%) | 0.88 | 0.96 (0.59 to 1.57) | -0.81 (-11.40 to 9.78) |

All analyses are intention to treat unless otherwise specified (assumes all participants with missing smoking status were smoking). Data are n (%) or n/N (%) unless otherwise specified. *Difference from χ^2 test. †Complete case analysis: excludes 64 participants with missing 6 month visits (withdrawn or lost to follow-up; 48 in nicotine e-cigarettes group and 16 in placebo e-cigarettes group) and includes 298 (241 in nicotine e-cigarettes group and 57 in placebo e-cigarettes group). ‡Per-protocol analysis 1: excludes protocol violations: pregnancy, death, quitters who did not have biochemical verification at 6 months, undisclosed medication ineligibility, withdrew, and lost to follow-up at 6 months. §Per-protocol analysis 2: excludes protocol violations from per-protocol analysis 1 plus: cross-overs, use of other or combined nicotine replacement therapy products, and use of non-nicotine replacement therapy (eg, varenicline). ¶Per-protocol analysis 3: excludes protocol violations from per-protocol analysis 2 plus: participants still using product to which they were randomised at 6 months. ||Continuous abstinence including not biochemically verified: eight participants in nicotine e-cigarettes group who reported quitting did not attend for biochemical verification (one moved, two refused, four did not attend appointment, one adverse event [birth] did not want to attend); one participant in the placebo e-cigarettes group did not attend appointment. **Output for repeated measures analysis is difference in least squares means (not relative risk).

Table 3: Continuous abstinence and 7 day point prevalence, nicotine e-cigarettes versus placebo e-cigarettes

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

Of 1293 people who were assessed, 657 were eligible for inclusion in the study (figure 1). 289 people were assigned to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes. Participants' baseline characteristics were evenly balanced between treatment groups (table 1). Overall, loss to follow-up was 22%: 17% (48 of 289) in the nicotine e-cigarettes group, 27% (80 of 295) in the patches group, and 22% (16 of 73) in placebo e-cigarettes group.

Verified continuous abstinence at 6 months after quit day was highest in the nicotine e-cigarettes group (7.3%), followed by the patches group (5.8%), and placebo e-cigarettes group (4.1%; tables 2, 3). Achievement of abstinence was substantially lower than we anticipated, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. 7 day point prevalence abstinence was closer to our estimate of 20%, and the RR suggested

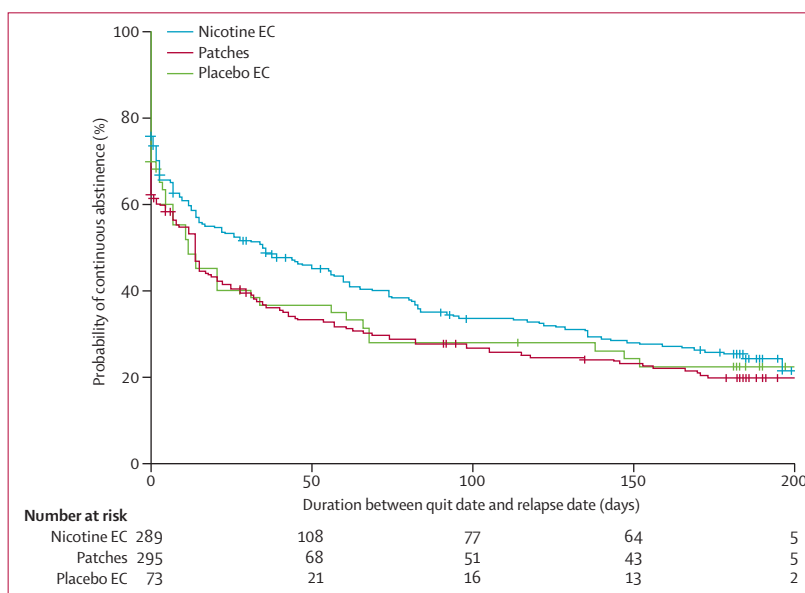


Figure 2: Kaplan-Meier analysis of time to relapse
EC=e-cigarettes.

a difference in favour of nicotine e-cigarettes, but was not significant at 6 months. Repeated measures analyses at 1 month and overall also showed a benefit of nicotine e-cigarettes compared with patches (table 2). However, both the point prevalence and repeated measures analyses used self-reported cessation. Subgroup analyses stratified by sex or ethnicity showed no significant differences in primary outcome (data not shown).

Quit rates were initially high then decreased in all groups (figure 2). Most participants relapsed within 50 days. Among those who relapsed, median time to relapse in the nicotine e-cigarettes group was 35 days (95% CI 15–56), more than twice as long as in the patches group (14 days, 95% CI 8–18, $p<0.0001$) or placebo e-cigarettes group (12 days, 5–34, $p=0.09$). Mean cigarette consumption decreased by two cigarettes per day more in the nicotine e-cigarettes group than the patches group ($p=0.002$; table 4). In the nicotine e-cigarettes group, 57% of participants reduced daily cigarettes by at least half at 6 months—a significantly greater proportion than in the patches group (41%; $p=0.0002$) and

non-significantly higher than in the placebo e-cigarettes group (45%; $p=0.08$).

Over 6 months, AUTOS scores in the e-cigarettes groups halved from baseline compared with a decrease of a third in the patches group (data not shown). The difference between the nicotine e-cigarettes group and patches group in total AUTOS score reduction from baseline to 6 months was significant (1.56, $p=0.02$), but the difference between the nicotine e-cigarettes group and placebo e-cigarettes group was not significant (1.34, $p=0.19$). Behavioural dependence, as measured by GN-SBQ, was balanced at baseline, with 36% (105 of 289) of participants in the nicotine e-cigarettes group, 37% (109 of 295) in the patches group, and 42% (31 of 73) in the placebo group scoring “strong” or “very strong” dependence, but we identified no association between score and outcome (data not shown).

A higher number and proportion of adverse events occurred in the nicotine e-cigarettes group than in the patches group (table 5); however, we identified no evidence of an association with study product, and the event rate was not significantly different (incidence rate ratio for nicotine e-cigarettes vs patches 1.05, 95% CI 0.82–1.34, $p=0.7$).

Adherence to study treatments was significantly higher in the nicotine e-cigarettes group compared with the patches group ($p<0.0001$ at each follow-up assessment) and with the placebo e-cigarettes group ($p<0.0001$ at each follow-up assessment): at 1 month post quit day, 78% (203 of 260) of participants in the nicotine e-cigarettes group and 82% (51 of 62) of those in the placebo e-cigarettes group were using the allocated product, compared with 46% (107 of 232) of those allocated to patches. By 3 months, 51% (126 of 245) participants in the nicotine e-cigarettes group and 53% (31 of 59) of those in the placebo e-cigarettes group were still using allocated treatments, compared with only 18% (40 of 224) of those in the patches group; at 6 months, 29% (71 of 241) of the nicotine e-cigarettes group and 35% (20 of 57) of the placebo e-cigarettes group persisted with e-cigarette use, with only 8% (17 of 215) of those in the patches group still using patches. Among those in the nicotine e-cigarettes group verified as abstinent, 38% (eight of 21) still used e-cigarettes at 6 months; among non-quiters, 29% (63 of 220) still used e-cigarettes (whether nicotine e-cigarettes or placebo e-cigarettes is unclear). Since average daily use was low, some participants could have been using cartridges allocated at randomisation, others might have purchased cartridges online. Participants using nicotine e-cigarettes reported having used an average of 1.3 cartridges per day at 1 month, 1.1 per day at 3 months, and 0.7 per day at 6 months; in the placebo group participants reported using 1.1 cartridges per day at 1 month, 1.2 per day at 3 months, and 0.7 per day at 6 months. Nicotine patches were used as instructed (an average of one per day). Few participants used other cessation products: at 6 months, in both the nicotine

| | Nicotine e-cigarettes | | Patches | | Difference (nicotine e-cigarettes–patches) | | |
|----------|-----------------------|-----|---------|-----|--|-----|---------|
| | Mean | SE | Mean | SE | Mean | SE | p value |
| Overall | 11.1 | 0.4 | 9.1 | 0.4 | 2.0 | 0.5 | <0.0001 |
| 1 month | 12.9 | 0.4 | 10.5 | 0.4 | 2.4 | 0.6 | <0.0001 |
| 3 months | 10.8 | 0.4 | 9.1 | 0.4 | 1.7 | 0.6 | 0.006 |
| 6 months | 9.7 | 0.4 | 7.7 | 0.4 | 1.9 | 0.6 | 0.002 |

*For those reporting smoking at least one cigarette in past 7 days.

Table 4: Change from baseline in cigarettes consumed per day during follow-up period, nicotine e-cigarettes and patches*

| | Nicotine e-cigarettes | | Patches | | Placebo e-cigarettes | |
|-----------------------------|-----------------------|-------|---------|-------|----------------------|-------|
| | N | % | N | % | N | % |
| Total | 137 | 100% | 119 | 100% | 36 | 100% |
| Event type | | | | | | |
| Serious* | 27 | 19.7% | 14 | 11.8% | 5 | 13.9% |
| Any non-serious event | 110 | 80.3% | 105 | 88.2% | 31 | 86.1% |
| Relation to study treatment | | | | | | |
| Definitely | 0 | | 1 | 0.8% | 0 | |
| Probably | 1 | 0.7% | 1 | 0.8% | 1 | 2.8% |
| Possibly | 5 | 3.6% | 4 | 3.4% | 1 | 2.8% |
| Unrelated | 131 | 95.6% | 113 | 95.0% | 34 | 94.4% |

107 participants in the nicotine e-cigarettes group had a total of 137 events. 96 participants in the patches group had a total of 119 events. 26 participants in the placebo group had a total of 36 events. Event rate was 0.8 events per person month in nicotine e-cigarettes group and patches group, and 0.9 in placebo e-cigarettes group. The difference between the rates in the nicotine e-cigarettes group and patches group were not significant (incidence rate ratio 1.05, 95% CI 0.82–1.34, $p=0.7$). *Serious adverse event by convention includes: death ($n=1$, in nicotine e-cigarettes group), life threatening illness ($n=1$, in nicotine e-cigarettes group), admission to hospital or prolongation of hospital stay (12% of all events in nicotine e-cigarettes group, 8% in patches group, and 11% in placebo e-cigarettes group), persistent or significant disability or incapacity, congenital abnormality, medically important (6% of all events in nicotine e-cigarettes group, 4% in patches group, and 3% placebo e-cigarettes group). No serious adverse events in any groups were related to product use.

Table 5: Adverse events by type (serious or non-serious) and relation to study treatment

e-cigarettes group and patches group, two participants had used bupropion and five had used varenicline in the past month; in the placebo e-cigarettes group, three participants reported using varenicline.

Quitline support was accessed by fewer than half of participants: 40% (115 of 289) in the nicotine e-cigarettes group, 36% (106 of 295) in the patches group, and 36% (26 of 73) in the placebo e-cigarettes groups, but a post-hoc analysis showed no benefit of use of support on the primary outcome for participants in the nicotine e-cigarettes group ($p=0.67$) or patches group ($p=0.16$).

There was sustained enthusiasm for e-cigarettes: at 1 month, 88% (230 of 260) of participants in the nicotine e-cigarettes group, and 92% (57 of 62) in the placebo e-cigarettes group stated that they would recommend their allocated product to a friend wanting to quit, compared with 56% (130 of 232) of those in the patches group; at 6 months the figures changed little, being 85% (205 of 241), 88% (50 of 57), and 50% (107 of 215), respectively. Among participants allocated to e-cigarettes, 40% (96 of 241) liked their tactile, cigarette-like qualities, sensory familiarity, perceived health benefits, taste, absence of cigarette odour, and ease of use.

Discussion

13 weeks of nicotine e-cigarette use resulted in increased smoking abstinence at 6 months compared with use of patches or placebo e-cigarettes, but these differences were not statistically significant. Nevertheless, the results were consistent across a range of analyses, and the 95% CIs do not exclude an advantage. In post-hoc analyses using a 5% non-inferiority limit for the risk difference (on the basis of a margin used in our non-inferiority smoking cessation trial of cytisine²⁶), nicotine e-cigarettes were at least as effective as patches (the absolute risk difference for the primary outcome was 1.51 [95% CI -2.49 to 5.51]; -2.49 is within the margin of -5). Therefore, we conclude that among smokers wanting to quit, nicotine e-cigarettes might be as effective as patches for achieving cessation at 6 months. We identified no difference in adverse events with e-cigarettes compared with patches.

The strengths of our study include use of a conservative primary outcome measure, and rigorous trial conduct to mitigate risk of bias. We used a pragmatic design because we believe that an assessment of real-world effectiveness of e-cigarettes is a priority for policy development, although it could be argued a trial of a novel intervention should be more explanatory than pragmatic in design. Our study had several limitations. First, the effect size and estimates of abstinence on which the study sample size was calculated were optimistic; hence, statistical power to detect differences was reduced. Second, participants assigned to patches had a higher loss to follow-up and withdrawal rate than those assigned to e-cigarettes. Some of the participants might have agreed to take part in the study to try e-cigarettes, and then lost interest when randomised to

Panel: Research in context

Systematic review

We searched Medline, PsycINFO, CINAHL, Embase, and the Cochrane library using the terms "e-cig*" OR "elect* cigar*" OR "electronic nicotine", for reports published between Jan 1, 2005, and Aug 23, 2013. The strategy identified 186 articles, of which only one was a randomised, placebo-controlled trial with a cessation endpoint measured at 6 months or more.⁹ This previous trial,⁹ done between 2011 and 2012, recruited 300 adult Italian smokers unwilling to quit, with 100 randomised to each of three groups: 7.2 mg nicotine cartridges for 12 weeks, 6 weeks of 7.2 mg cartridges followed by 6 weeks of 5.4 mg cartridges, and 0 mg nicotine cartridges for 12 weeks. No behavioural support was provided but nine follow-up visits occurred, with carbon monoxide measures at each. The primary outcome was not clearly prespecified nor were calculations done to estimate power. Analysis was by intention to treat. At 12 months, 39% of participants had been lost to follow-up, a potential source of bias. Of those assessed, 9% had quit (13%, 9%, and 4% in the two nicotine e-cigarettes groups and placebo e-cigarettes groups, respectively) and reduction occurred in 10%, 9%, and 12%; none of the comparisons were statistically significant. The reliability of e-cigarettes was problematic. These results are much the same as those reported in previous trials of unsupported pharmacotherapy with patches³² and are similar to our trial findings.

Interpretation

In our study, e-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit. Nicotine e-cigarettes might be more effective or of similar effectiveness to patches, but so far studies have not had sufficient statistical power to draw more definitive conclusions. E-cigarette use was associated with few adverse events, similar to patches, but longer-term data are needed. Uncertainty exists about the place of e-cigarettes in tobacco control, and more research is urgently needed to clearly establish their overall benefits and harms at both individual and population levels.

patches. Those who reported previously trying to quit with patches or other forms of NRT (about 20% in the past year in each group) might have disadvantaged patches (by being more likely to give up on patches subsequently); however, at 6 months the difference between the results of the intention-to-treat analysis and per-protocol analysis was minimal, suggesting this bias was not a major issue.

Third, the modest abstinence rate for nicotine e-cigarettes is much the same as quit rates shown in studies of NRT products used without behavioural support.²⁷ Addition of more intensive support might have improved quit rates, but it would also have misrepresented the typically low support environment in which most e-cigarette users attempt to quit. The modest abstinence rates might have been compounded by inadequate nicotine replacement: as noted, the cartridges contained less nicotine than labelled, and delivery was inefficient (not uncommon in other early e-cigarette models^{15,28}). Furthermore, users consumed on average just over one cartridge per day, delivering around only 20% of the nicotine obtained from cigarette smoking.²⁹ Although trials of the effects of early e-cigarettes on withdrawal relief showed that low levels of nicotine delivery attenuated withdrawal symptoms,^{7,8} improved nicotine delivery by newer models of e-cigarettes provides greater withdrawal relief,

potentially enhancing cessation effectiveness.⁸ Trials of such second generation e-cigarettes are needed.

We included the placebo e-cigarettes group to explore the role of behavioural replacement by e-cigarettes, independent of nicotine delivery in cessation.³⁰ However, our study was underpowered to detect the small effect, and the GN-SBQ instrument, which purports to measure behavioural dependence but has not been widely used in this context, might have been inadequate for this purpose.

A third of the participants allocated to the e-cigarettes groups reported continued product use at 6 months, suggesting that they might have become long-term e-cigarette users. Those who had relapsed to smoking but continued to use e-cigarettes (so called dual use) at 6 months had reduced cigarette consumption. Research has shown higher cessation rates in people using NRT while still smoking;³¹ if e-cigarettes act in the same way this would be a positive feature. Further research is needed to explore this area.

Finally, as far as we are aware, our trial provides for the first time adverse event information for 657 people randomly allocated to e-cigarettes or patches. The finding of no significant differences in occurrence of adverse events between groups over the duration of a standard NRT treatment course, and the further 3 months' monitoring, suggests such short-term e-cigarette use is of low risk. However, longer-term use requires more research (panel).

Our study has established benchmarks for performance of nicotine e-cigarettes relative to NRT and placebo e-cigarettes with which to design future, more adequately powered trials. Our findings point to potential for e-cigarettes in regard to cessation effectiveness beyond that noted in the present study. Furthermore, because they have far greater reach^{1,2} and higher acceptability (as shown by the present study) among smokers than NRT, and seem to have no greater risk of adverse effects, e-cigarettes also have potential for improving population health.

Contributors

CB, NW, HM, and ML conceived the original idea for the trial, and sought and obtained funding. CB, NW, HM, ML, CH, VP, and JW wrote the study protocol. CH managed the day-to-day running of the trial, including all participant follow-up. VP did the data analyses. This Article was written by CB with input from all coauthors. CB is guarantor for this Article. All authors read and approved the final version.

Conflicts of interest

We declare that we have received no support from any companies for the submitted work and have no non-financial interests that might be relevant to the submitted work. ML, via his company Health New Zealand, previously did research funded by Ruyan (an e-cigarette manufacturer). CB and HM have done research on Ruyan e-cigarettes funded by Health New Zealand, independently of Ruyan. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications.

Acknowledgments

The e-cigarettes and cartridges were Elusion brand products provided by PGM International, New Zealand. PGM International had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. We thank the participants, research assistants, our colleagues, the Health Research Council of New Zealand, PGM International, and New Zealand Quitline.

References

- Purkayastha D. BAT ramps-up e-cigarette expansion as sales go up in smoke international business times (July 31, 2013). [http://www.thefreelibrary.com/BAT Ramps-up E-cigarette Expansion as Sales Go Up in Smoke.-a0338323170](http://www.thefreelibrary.com/BAT+Ramps-up+E-cigarette+Expansion+as+Sales+Go+Up+in+Smoke.-a0338323170) (accessed Aug 13, 2013).
- West R. Smoking toolkit study: monthly tracking of key performance indicators (July 20, 2012). <http://www.smokinginengland.info/latest-statistics/> (accessed Aug 9, 2013).
- Hajek P, Foulds J, Hounziec JL, Swenor D, Yach D. Should e-cigarettes be regulated as a medicinal device? *Lancet Respir Med* 2013; **1**: 429–31.
- Cobb N, Cobb C. Regulatory challenges for refined nicotine products. *Lancet Respir Med* 2013; **1**: 431–33.
- Etter J-F. Electronic cigarettes: a survey of users. *BMC Public Health* 2010; **10**: 231.
- Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction* 2013; **108**: 1115–25.
- Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010; **19**: 98–103.
- Vansickel A, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res* 2013; **15**: 267–70.
- Caponnetto P, Campagna D, Cibella F, et al. Efficiency and safety of an electronic cigarette (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS One* 2013; **8**: e66317.
- US Food and Drug Administration (FDA). Summary of results: laboratory analysis of electronic cigarettes conducted by FDA. <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm> (accessed Aug 9, 2013).
- Goniewicz M, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2013; **6**: 6.
- Burstyn I. Peering through the mist: what does the chemistry of contaminants in electronic cigarettes tell us about health risks? Technical report. <http://publichealth.drexel.edu/SiteData/docs/ms08/f90349264250e603/ms08.pdf> (accessed Aug 13, 2013).
- Bullen C, Williman J, Howe C, et al. Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. *BMC Public Health* 2013; **13**: 210.
- Heatherton T, Kozlowski L, Frecker R, Fagerstrom K. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. *Br J Addict* 1991; **86**: 1119–27.
- Goniewicz M, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 2013; **15**: 158–66.
- Price E, Allen M. New Zealand: effective access to tobacco dependence treatment. WHO, 2003. http://www.who.int/tobacco/research/cessation/en/best_practices_new_zealand.pdf (accessed Sept 4, 2013).
- Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012; **11**: CD000146.
- Ministry of Health. New Zealand smoking cessation guidelines. Wellington: Ministry of Health, 2007.
- DiFranza J, Wellman R, Ursprung W, Sabiston C. The autonomy over smoking scale. *Psychol Addict Behav* 2009; **23**: 656–65.
- Glover E, Nilsson F, Westin A, Glover P, Laffin M, Persson B. Developmental history of the Glover-Nilsson smoking behavioral questionnaire. *Am J Health Behav* 2005; **29**: 443–55.
- West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005; **100**: 299–303.

- 22 Ursprung W, Morello P, Gershenson B, DiFranza J. Development of a measure of the latency to needing a cigarette. *J Adolesc Health* 2011; **48**: 338–43.
- 23 Fiore M, Jaen C, Baker T, et al. Treating tobacco use and dependence: 2008 update. Rockville, MD: US Department of Health and Human Services, Public Health Service, 2008.
- 24 Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**: c332.
- 25 Cormack D, Robson C. Classification and output of multiple ethnicities: considerations for monitoring Māori health. Wellington: Te Rōpū Rangahau Hauora a Eru Pōmare, 2010.
- 26 Walker N, Howe C, Bullen C, et al. Study protocol for a non-inferiority trial of cytosine versus nicotine replacement therapy in people motivated to stop smoking. *BMC Public Health* 2011; **11**: 880.
- 27 Shiffman S, Rolf C, Hellebusch S, et al. Real-world efficacy of prescription and over-the-counter nicotine replacement therapy. *Addiction* 2002; **97**: 505–16.
- 28 Polosa R, Morjaria J, Caponnetto P, et al. Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med* 2013; published online July 20. DOI:10.1007/s11739-013-0977-z.
- 29 Mariner D, Ashley M, Shepperd C, Mullard G, Dixon M. Mouth level exposure using analysis of filters from smoked cigarettes: A study of eight countries. *Regul Toxicol Pharmacol* 2011; **61**: S39–50.
- 30 Caponnetto P, Cibella F, Mancuso S, Campagna D, Arcidiacono G, Polosa R. Effect of a nicotine-free inhalator as part of a smoking-cessation programme. *Eur Respir J* 2011; **38**: 1005–11.
- 31 Fagerstrom K, Tejding R, Westin A, Lunell E. Aiding reduction of smoking with nicotine replacement medications: hope for the recalcitrant smoker? *Tob Control* 1997; **6**: 311–16.
- 32 Stead L, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012; **11**: CD000146.