



Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial

C Bullen, H McRobbie, S Thornley, et al.

Tob Control 2010 19: 98-103

doi: 10.1136/tc.2009.031567

Updated information and services can be found at:

<http://tobaccocontrol.bmj.com/content/19/2/98.full.html>

These include:

References

This article cites 12 articles, 4 of which can be accessed free at:

<http://tobaccocontrol.bmj.com/content/19/2/98.full.html#ref-list-1>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:

<http://tobaccocontrol.bmj.com/cgi/reprintform>

To subscribe to *Tobacco Control* go to:

<http://tobaccocontrol.bmj.com/subscriptions>

Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial

C Bullen,¹ H McRobbie,² S Thornley,³ M Glover,⁴ R Lin,⁵ M Laugesen⁶

¹Clinical Trials Research Unit, The University of Auckland, Auckland, New Zealand

²Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

³Section of Epidemiology and Biostatistics, The University of Auckland, Auckland, New Zealand

⁴Centre for Tobacco Control Research, The University of Auckland, Auckland, New Zealand

⁵Biometric, Covance Pty Ltd, Sydney, Australia

⁶Health New Zealand Ltd, Christchurch, New Zealand

Correspondence to

Dr Christopher Bullen, Clinical Trials Research Unit, The University of Auckland, Private Bag 92019, Auckland, New Zealand; c.bullen@ctr.u.auckland.ac.nz

Received 15 May 2009

Accepted 2 December 2009

ABSTRACT

Objectives To measure the short-term effects of an electronic nicotine delivery device ("e cigarette", ENDD) on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects.

Design Single blind randomised repeated measures cross-over trial of the Ruyan V8 ENDD.

Setting University research centre in Auckland, New Zealand.

Participants 40 adult dependent smokers of 10 or more cigarettes per day.

Interventions Participants were randomised to use ENDDs containing 16 mg nicotine or 0 mg capsules, Nicorette nicotine inhalator or their usual cigarette on each of four study days 3 days apart, with overnight smoking abstinence before use of each product.

Main outcome measures The primary outcome was change in desire to smoke, measured as "area under the curve" on an 11-point visual analogue scale before and at intervals over 1 h of use. Secondary outcomes included withdrawal symptoms, acceptability and adverse events. In nine participants, serum nicotine levels were also measured.

Results Over 60 min, participants using 16 mg ENDD recorded 0.82 units less desire to smoke than the placebo ENDD ($p=0.006$). No difference in desire to smoke was found between 16 mg ENDD and inhalator. ENDDs were more pleasant to use than inhalator ($p=0.016$) and produced less irritation of mouth and throat ($p<0.001$). On average, the ENDD increased serum nicotine to a peak of 1.3 mg/ml in 19.6 min, the inhalator to 2.1 ng/ml in 32 min and cigarettes to 13.4 ng/ml in 14.3 min.

Conclusions The 16 mg Ruyan V8 ENDD alleviated desire to smoke after overnight abstinence, was well tolerated and had a pharmacokinetic profile more like the Nicorette inhalator than a tobacco cigarette. Evaluation of the ENDD for longer-term safety, potential for long-term use and efficacy as a cessation aid is needed.

Trial registration No.12607000587404, Australia and New Zealand Clinical Trials Register

Nicotine replacement therapies (NRTs) are safe and effective aids for smoking cessation¹; however, they remain underutilised.² To widen their appeal to smokers, a variety of effective NRTs and cigarette smoking alternatives are needed. In 2004, a Beijing-based company, Ruyan Group (Holdings) Ltd, China, patented and launched an electronic nicotine delivery device (ENDD) or "e-cigarette",³ a battery-powered device resembling a cigarette that contains

a microelectrical circuit activated by drawing on the mouthpiece. With each puff, a small amount of nicotine-propylene glycol solution contained in replaceable cartridges is heated and vapourised, to create a visible mist without smoke or flame. Manufacturers now export a growing number and variety of these devices to industrialised countries. People report buying them to help quit smoking, to reduce cigarette consumption and costs, to relieve tobacco withdrawal symptoms due to workplace smoking restrictions, or as a replacement for cigarette smoking.⁴

Although ENDD use has not been comprehensively studied, to our knowledge, no deaths or hospitalisations from ENDD use have been reported. Analyses of emissions of the Ruyan V8 ENDD suggest a low risk of toxicity (M Laugesen, 2009, TC2009/034355, submitted). The risk of impurities in the cartridge liquid is, however, of concern to the US Food and Drug Administration,⁵ and there is a lack of internationally certified manufacturing sites. Regulators also lack data on the ability of ENDDs to relieve the desire to smoke cigarettes and to suppress other tobacco withdrawal symptoms. Study designs that assess change in subjective withdrawal symptoms have been used to evaluate the utility of other novel nicotine delivery devices.^{6–8} Using such an approach, this study compared the Ruyan V8 ENDD containing 16 mg nicotine cartridges to one containing 0 mg cartridges (identical in appearance and in chemistry but lacking nicotine), Nicorette nicotine inhalator and usual cigarettes. We measured change in desire to smoke, withdrawal symptoms, product preferences, serum nicotine levels and adverse events after 1 day's use.

METHODS

Participants

Participants were recruited from the local community in Auckland, New Zealand, between January 2008 and February 2008. They were assessed via an initial telephone call for eligibility (aged between 18 and 70 years, smoked 10 or more factory-made cigarettes per day for at least the past year, smoked their first cigarette of the day within 30 min of waking, and were not currently attempting to quit smoking or wishing to do so in the next 30 days). Eligible participants were invited to visit the study centre at The University of Auckland to give written informed consent, complete a questionnaire asking about demographic and smoking

characteristics and undergo screening (medical history, blood pressure, heart rate and urinalysis for glucose). We excluded people who reported recent myocardial infarction, angina pectoris or other serious medical conditions (diabetes mellitus, severe allergies, poorly controlled asthma or other airways disease, poorly controlled psychiatric disorders or current chemical dependence other than nicotine) and pregnancy (confirmed by positive urinary dipstick for β HCG), breastfeeding, blood pressure >180 mm Hg systolic and/or 100 mm Hg diastolic, weight <45 or >120 kg, or current use of any other smoking cessation medications. At this time, we invited all participants to indicate if they were also willing to give venous blood samples for analysis of nicotine.

Study medication

Ruyan V8 ENDDs supplied by the manufacturer, Ruyan Group (Holdings) Ltd, are pen-shaped devices that include a rechargeable lithium ion battery, an electronic circuit, a vaporiser, a replaceable cartridge and a mouthpiece. The cartridge labelled 16 mg contains 1.06 g of liquid comprising 8.8% water, 1.4% nicotine, 89.7% propylene glycol and 0.1% glycol (M Laugesen, 2009, TC2009/034355, submitted). Participants randomised to a day using the ENDD were asked to puff the device as they would their usual cigarette for 5 min. After the first hour, they left the study centre and used the device as required for a further 8 h before returning to complete the rating scales. We charged all batteries 2 weeks before the study and between each day of use to ensure they would operate as intended. Nicorette inhalators (manufactured at the time of the study by Pfizer Health AB, Helsingborg, Sweden) were purchased commercially. When participants used the inhalator, we gave them a blister pack of six inhalator cartridges, each containing 10 mg of nicotine for inhalation, with instructions to puff on the inhalator over 20 min in the first hour. Thereafter, they were instructed to use it freely, preferably hourly, up to a maximum of six cartridges over the day, as recommended by the manufacturer,⁹ before returning to the study centre. When randomised to smoke their usual cigarettes, participants did so over the first 5 min in the first hour, then freely as they wished.

Sample size

Based on a previous study,¹⁰ we estimated 48 participants would be needed to detect a one-point difference in desire to smoke on an 11-point (0–10) scale measured at 20 min, for the comparison between the 16 and 0 mg ENDD, assuming a within-participant SD of the response variable of 1.5 points and statistical power of 90% at a two-sided significance level of 5%.

Procedures

Participants were requested to abstain from smoking and alcohol from 20:00 on the night before each study day and from food and caffeine for at least 1 h before the session. On arrival at the study centre, carbon monoxide (CO) was measured in participants' expired breath using a Bedfont Smokelyser.¹¹ If CO was ≤ 15 parts per million (ppm), the assigned study treatment was allocated; however, if CO was >15 ppm or they reported smoking in the previous 12 h, participants were rescheduled wherever possible to a subsequent session. On the first study day, participants were randomised to use one of four different products: ENDDs containing nicotine (16 mg) or placebo (0 mg) capsules, Nicorette nicotine inhalator or their usual cigarette. Allocation was performed using a random sequence of four codes, each corresponding to one product, prepared in advance by the study statistician using the Latin-square method to

control for time effects. Participants and investigators were blinded only to assignment to the ENDD condition (16 or 0 mg), and it was not possible to change the order of treatment allocation. Participants sat at desks in a room where they completed ratings of desire to smoke and other withdrawal symptoms 15 and 5 min before using their allocated product (these ratings were later averaged to provide baseline ratings). They rinsed their mouth with water (to equalise oral pH) and took their first dose at 08:30. When allocated to smoke their usual cigarettes, participants did so outside (required by law); however, when allocated to the ENDDs, participants used them indoors. Ratings were made at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min counting from the first puff on each product. Participants then left the study centre with instructions to continue their usual daily activities but not to smoke (unless in the usual cigarette group) and to use the study product regularly and freely throughout the day. They returned at 17:30 for CO measurement, to report product use including adverse events and the number of any cigarettes smoked, rate the degree of satisfaction and usefulness, and to return the remaining study product. Participants were allowed to smoke as they wished once these measures were collected and during the 3-day washout period between each study day. On the day allocated for using their own cigarette, participants did not take part in evening measurements.

A subset of participants gave venous blood samples for analysis of plasma nicotine concentrations. In this group, in addition to the procedures described above, on each study day, medical staff inserted an 18-gauge butterfly needle in a non-dominant forearm vein and withdrew 5-ml blood samples at baseline, then at 5, 10, 15, 30 and 60 min after initial dosing. Blood samples were held in vacuum tubes in a temperature-monitored cool box maintained between 0°C and 6°C and at the end of each study session were transported to a local laboratory for separation. The plasma fraction was frozen before being shipped to a national reference laboratory for nicotine concentration assay using the method developed by Mahoney and Al-Delaimy.¹²

Following study completion, participants were invited to attend a group cessation clinic run over 5 weeks. The majority attended at least one of these sessions.

Measures

We assessed withdrawal using three items from the Minnesota Nicotine Withdrawal Scale¹³: irritability, restlessness and difficulty concentrating. The other Minnesota Nicotine Withdrawal Scale items—increased appetite/weight gain, depression or insomnia—were not included because these would not be plausibly experienced in such a short period. We included an additional item, “desire to smoke” (a cigarette), a construct equivalent to the more commonly used terms “craving” or “urges”,¹⁴ which was measured by asking, “Right now, how much do you want a cigarette?” We asked participants to indicate their perception of all items by circling a visual analogue scale number between 0 and 10, where 0=“not at all” and 10=“extremely”. Participants noted the occurrence of adverse events commonly experienced with NRT use using categories adapted from Hajek *et al*¹⁵ and any other reactions not on this list. On the last study day, still blind to the ENDD condition, participants were asked to rate their satisfaction with the products compared to their usual cigarettes using scales (0=“completely unsatisfying”, 10=“fully satisfying”)¹⁵; on the same scale, they rated helpfulness (in keeping them from smoking), how pleasant the product was to use, how embarrassing it was to use in the company of others, the degree to

Research paper

which they would use it to aid a quit attempt, and whether they would recommend it to a friend who wanted to stop smoking.

Statistical analysis

All analyses were undertaken on an intention-to-treat basis. We analysed the primary outcome, comparison of change in desire to smoke between the 16 and 0 mg ENDD, using area under the curve over 60 min as the dependent variable. The treatment effect was thus the average change in desire to smoke over the 60 min after first using each product. For this and the other ratings, the baseline score (the area under the curve at 5 min before product use), treatment effect and time period were fixed effects in the model. We also examined the change in desire to smoke between the ENDD and other products (inhalator and usual cigarette) using analysis of covariance with within-participant variation included as a random effect. We dealt with missing data using the last value carried forward method. Pharmacokinetic parameters (C_{max} (peak plasma concentration) and t_{max} (time to reach C_{max})) were calculated based on plasma concentration-time data by model-independent methods using SAS version 9.2 (SAS Institute). Multiple comparisons between products were adjusted for using the Tukey-Kramer method and p values and 95% confidence intervals (CIs) were estimated for each comparison.

RESULTS

Participant characteristics

Figure 1 shows participant flow. Forty participants were randomised, 53% of whom were women. The mean age was 47.6 (SD 12.4) years and the mean level of nicotine dependence (Fagerström Test of Nicotine Dependence¹⁶) was 5.4. Participants smoked an average of 20.2 (SD 7.3) cigarettes smoked per day. Twenty-five participants had previously used nicotine patches, nineteen reported previously using nicotine gum, two had used the inhalator, but none had used an ENDD before. During the study days, most participants used the products regularly and abstained from smoking as instructed; however, when using the 16 mg ENDD, participants smoked on average 2.8 usual cigarettes over the day, compared with 4.5 cigarettes when using the 0 mg ENDD and 3.4 cigarettes when using the inhalator. Nine participants on average gave blood samples for pharmacokinetic analysis on each of 5 study days.

Desire to smoke and withdrawal symptoms

Figure 2 shows the change from baseline in desire to smoke over 60 min. Usual cigarette use resulted in significantly greater reductions in desire to smoke compared to ENDD (16 and 0 mg) and inhalator. Desire to smoke ratings reached their lowest level 5 min after the first puff with usual cigarettes, 10 min after the first puff with 0 mg ENDD, 15 min after first puff with 16 mg ENDD and on completing 20 min of puffing on the inhalator. Over the 60 min period, participants using the 16 mg ENDD experienced a greater decrease in desire to smoke (2.6 units) than participants using the 0 mg ENDD (1.8 units), a difference of 0.82 units (95% CI 0.25 to 1.38; $p=0.006$) (see table 1). In the comparisons between 16 and 0 mg ENDD at each time point, the difference in desire to smoke became significant from 25 min through to 60 min, when users recorded 1.3 units (95% CI 0.33 to 2.25, $p=0.009$) less desire to smoke with the 16 mg ENDD than the 0 mg ENDD.

Over 60 min, the use of the 16 mg ENDD reduced ratings for irritability, restlessness and difficulty concentrating more than the 0 mg ENDD; however, these differences were not statisti-

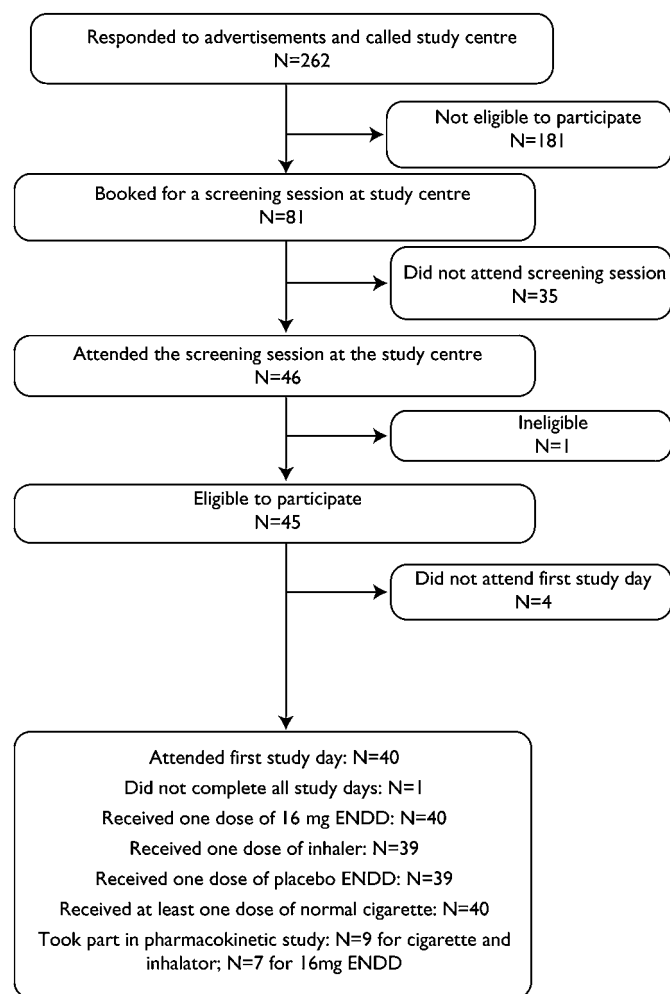


Figure 1 Participant flow.

cally significant (table 1). Similarly, there was no difference in withdrawal symptoms between the 16 mg ENDD and inhalator, whereas usual cigarettes reduced withdrawal ratings more on all items than the other products.

Results of the secondary analyses comparing the 16 mg ENDD, inhalator, usual cigarette and 0 mg ENDD are shown in table 2. Although a greater reduction in desire to smoke was observed with the 16 mg compared to the 0 mg cigarette, this difference was no longer significant when adjusted for multiple comparisons.

Product preferences

The 16 mg ENDD rated higher for pleasantness of use than the inhalator, by 1.49 units (95% CI 0.23 to 2.74, $p=0.016$). Figure 3 shows that mean satisfaction ratings for 16 mg ENDD and inhalator were similar and were higher than those for placebo ENDD, and embarrassment associated with using the device in the company of others was low but not significantly different to the inhalator. The 16 mg ENDD was favoured over other products for enabling participants to keep from smoking, to be used as a potential quitting aid and for recommending to a friend who wanted to stop smoking. It was also the most preferred alternative to cigarettes: 58% of participants said they preferred the ENDD, 25% preferred the inhalator and 13% liked neither. The degree of ease of use was similar for ENDD and inhalator (48% and 45%, respectively).

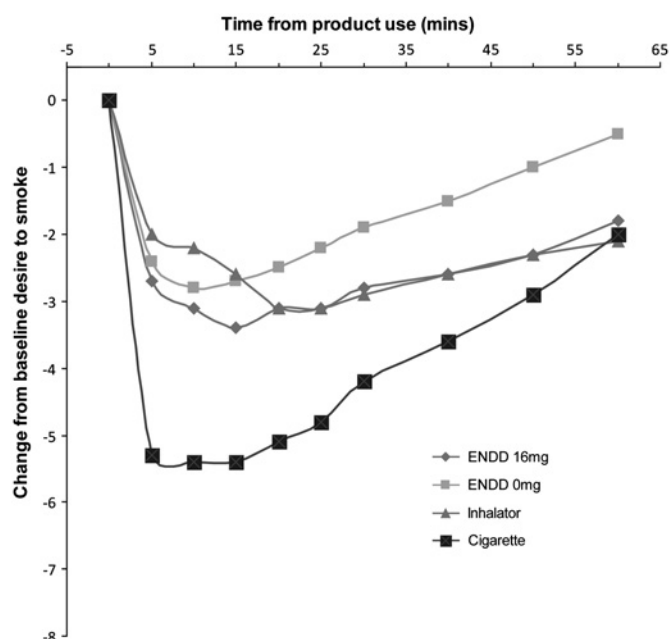


Figure 2 Change in desire to smoke from baseline over the first hour after each product use.

Pharmacokinetics

On average, the use of the 16 mg ENDD resulted in modest increases in blood nicotine levels (see table 3). The fastest time to peak nicotine concentration was obtained with usual cigarettes, followed by nicotine ENDDs and the inhalator. Usual cigarette use gave a significantly higher C_{max} than the other products in the individual product and crossover analysis, with adjustment for multiple comparisons ($p=0.01$).

Adverse events

The most frequently reported adverse events were mouth and throat irritation (table 4), and were most common with the inhalator (88%) and least common with the 0 mg ENDD (22%). The differences between active and placebo ENDDs and inhalator were statistically significant ($p<0.001$). Nausea was most commonly reported after 16 mg ENDD use, but, as with the other between-product differences in adverse events occurrence, was not significant. No serious adverse events (ie, deaths or events requiring hospitalisation) occurred during the study.

DISCUSSION

The 16 mg Ruyan ENDD was significantly more effective than the 0 mg ENDD at reducing desire to smoke over 1 h of use. The 0 and 16 mg ENDD relieved desire to smoke within the first 10 min of use, but the 16 mg ENDD reduced desire to smoke most at 15 min (10 min after the last puff), more than either the 0 mg ENDD or the nicotine inhalator, which was still being puffed as per instructions given to participants. The reduction in

Table 1 Primary comparisons of change in desire to smoke and other withdrawal symptoms from baseline between 0 and 16 mg nicotine ENDD

Withdrawal symptom*	Mean change (95% CI)	p Value
Desire to smoke	0.82 (0.25 to 1.38)	0.006
Irritability	0.26 (−0.48 to 0.99)	0.48
Restlessness	0.53 (−0.11 to 1.18)	0.10
Poor concentration	0.39 (−0.30 to 1.07)	0.26

*Visual analogue scale 0 to 10.

Table 2 Secondary analyses using multivariate* comparisons of change in desire to smoke from baseline between all products

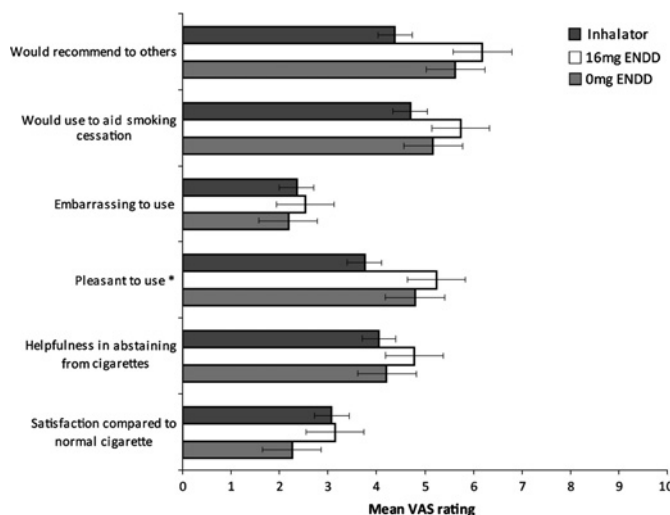
Product comparison	Mean difference (95% CI)	Adjusted p value
0 versus 16 mg ENDD	0.80 (−0.27 to 1.86)	0.21
0 mg ENDD versus Nicorette inhalator	0.69 (−0.38 to 1.77)	0.33
0 mg ENDD versus usual cigarette	2.23 (1.17 to 3.30)	<0.0001
16 mg ENDD versus Nicorette inhalator	−0.10 (−1.16, 0.95)	0.99
16 mg ENDD versus usual cigarette	1.44 (0.39 to 2.48)	0.003
Nicorette inhalator versus usual cigarette	1.54 (0.48 to 2.59)	0.001

ENDD, electronic nicotine delivery device.

*Adjusted for treatment period, baseline craving, within-participant correlation as a random effect and multiple comparisons using Tukey-Kramer method.

desire to smoke in the first 10 min of ENDD use appears to be independent of nicotine absorption, and may be due to behavioural and oral and tactile sensations similar to cigarette smoking, and the anticipation of nicotine delivery.

In the pharmacokinetic analyses, the serum nicotine C_{max} for usual cigarettes was comparable with other studies.¹⁷ The 16 mg ENDD's performance was consistent with findings from intensive-mode smoking machine tests of this same make of ENDD, which delivered 10% of the nicotine per puff delivered by a regular Marlboro cigarette (M Laugesen, 2009, TC2009/034355, submitted). This suggests that it is more like a NRT product, concerning nicotine delivery, than a cigarette. The shorter t_{max} of the ENDD in comparison to the inhalator may reflect some absorption via the respiratory tract compared with buccal absorption for the Nicorette inhalator. The ENDDs in the study were not as consistent for puffing and nicotine delivery as the medicinal Nicorette inhalator. About one-third of participants showed no increase in blood nicotine when using the ENDD. Some participants reported that the device sometimes failed to produce mist when puffed. It is possible that technical problems could have affected the dose received. This is not altogether surprising given that these devices are not manufactured to the same standards required of pharmaceutical devices, such as the inhalator.



*Adjusted for treatment period, baseline craving, participant as random effect and multiple comparisons using Tukey method.

Figure 3 A higher rating is indicative of a greater likelihood of finding the product more satisfying, helpful, pleasant, embarrassing, likely to be used for aiding smoking cessation and to be recommended to others (error bars represent standard error).

Research paper

Table 3 Pharmacokinetic properties of usual cigarette, 16 mg ENDD and Nicorette inhalator

Product	Mean tmax (min) (95% CI)	Mean Cmax (ng/mL) (95% CI)*
Usual cigarette (n=9)	14.3 (8.8 to 19.9)	13.4 (6.5 to 20.3)
16 mg ENDD (n=8)	19.6 (4.9 to 34.2)	1.3 (0.0 to 2.6)
Nicorette inhalator (n=10)	32.0 (18.7 to 45.3)	2.1 (1.0 to 3.1)

ENDD, electronic nicotine delivery device.

*Corrected for baseline nicotine levels.

We also noted that three participants (one using the inhalator, two using ENDDs) had high baseline serum nicotine values (12.8, 12.0 and 6.6 ng/ml), which declined over the hour, raising the possibility of recent smoking of a tobacco cigarette, despite CO readings suggesting otherwise. Excluding these data in a post hoc analysis on the primary outcome and withdrawal symptoms gave a small increment in the mean decrease in desire to smoke, from 0.82 to 0.91 units (95% CI 0.29 to 1.53), which was still significant ($p=0.006$) compared to placebo, with little change to the values and significance of changes in irritability, restlessness and poor concentration.

Overall, the Ruyan ENDD was similar to the Nicorette inhalator on a range of subjective ratings of user preferences, and users reported a similar frequency of most adverse events except for a far lower occurrence of mouth or throat irritation than for the inhalator.

The strengths of this study include the study population of dependent but "healthy" male and female smokers recruited from the community; the use of a crossover design to minimise variability, bias and confounding; and the use of items from validated instruments for measuring key outcomes. We used a range of statistical tests including mixed model analysis, which has the advantage of including all the data and accounting for within-subject correlation.

The study has a number of limitations. First, it was statistically powered to detect a difference between 16 mg ENDD and 0 mg ENDD, not to detect a difference between 16 mg ENDD and inhalator, and the desired sample size of 48 was not achieved despite best endeavours to recruit to this target. Second, low baseline ratings of desire to smoke may have limited the degree of observable change. Third, the study was limited to smokers not intending to quit, which may underestimate the reduction in desire to smoke expected in smokers intending to quit. Fourth, this was the first experience for participants and investigators with the ENDD and there was no period of familiarisation with the products before use nor did we test them to ensure normal

Table 4 Adverse events reported by participants after 9 h of product use, by product

Adverse event	ENDD 0 mg		ENDD 16 mg		Nicorette inhalator	
	n/N*	(%)	n/N	(%)	n/N	(%)
Mouth/throat irritation†	14/64	22	22/58	38	36/41	88
Aching jaws	4/35	11	3/37	8	2/37	5
Nausea	6/33	18	9/31	29	6/33	18
Flatulence/belching/hiccups/heartburn	6/111	5	6/113	5	11/147	23
Vertigo/feeling high	9/69	9	14/66	21	12/66	18
Headache	7/32	22	6/34	18	6/33	18
Sweatiness/clammy skin	3/75	4	3/77	4	2/76	3
Palpitations	0/38	0	2/38	5	0/39	0

ENDD, electronic nicotine delivery device.

*n=number of events, N=numbers of participants in each group. In some cases, groups were pooled because of similarity of symptoms, hence the large numbers.

†ENDD 0 mg versus inhalator $p<0.001$; ENDD 16 mg versus inhalator $p<0.001$.

What this study adds

- ▶ The Ruyan 16 mg nicotine ENDD reduces desire to smoke.
- ▶ The ENDD has a pharmacokinetic profile more like the nicotine inhalator than a tobacco cigarette.
- ▶ Further research is needed on the pharmacokinetics, long-term use potential, safety, manufacturing quality and quitting efficacy associated with ENDD use.

functioning. Both factors could have affected the pharmacokinetic results and attenuated the ratings of desire to smoke. Fifth, the four-fold greater puffing time allowed for the inhalator is problematic for comparing products, as it is by no means clear yet whether an ENDD inhaling session should be for 5, 10 or 20 min a session. Finally, use of each study product for just 9 h did not allow sufficient time for assessment of delayed acute or chronic use effects, nor of the potential for long-term use.

CONCLUSIONS

The Ruyan V8 16 mg ENDD reduced desire to smoke more than the placebo ENDD and during 9 h of use was well tolerated, acceptable to most users, rated significantly more pleasant to use than the inhalator, and in the first hour exhibited a pharmacokinetic profile more like the inhalator than a tobacco cigarette, without excess adverse events. These findings suggest potential to help people stop smoking in the same way as a nicotine inhalator. Our findings should be regarded as preliminary and need to be confirmed for this and other brands of ENDD. The nicotine pharmacokinetics of ENDDs should be confirmed in other studies, and different ways of using these devices need to be explored. A large, well-conducted randomised trial is needed to evaluate the ENDD's efficacy as a quitting aid and to identify any delayed or long-term adverse effects.

Acknowledgements We thank the people who took part, and Joanne Lorimer, Denise Miller and Henry Bohte for their help in undertaking this study.

Funding This project was funded by Ruyan Group (Holdings) Limited, Beijing and Hong Kong, via Health New Zealand Ltd. The study sponsors supplied the ENDDs used in the trial and funded the trial. The Clinical Trials Research Unit contracted with Health New Zealand Ltd to conduct the trial, independently of Ruyan Group (Holdings) Ltd. The trial design conduct, analysis and interpretation of results were conducted independently of the sponsors.

Competing interests CB, ST and RL have no competing interests to declare. HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. ML acted as contract manager with the sponsor, Ruyan Group (Holdings) Limited, via his company Health New Zealand Ltd. ML and Health New Zealand Ltd have no patent, stock or other financial interest in Ruyan Group (Holdings) Limited or any nicotine or tobacco company. MG has provided consultancy to the manufacturers of smoking cessation medications.

Ethics approval Ethical approval for the trial was obtained from the New Zealand Ministry of Health's Northern Y Ethics Committee (approval number NTY/07/10/109).

Contributors CB, HM, ST, MG, RL and ML designed and conducted the study, interpreted the data, and wrote the manuscript. CB, HM and ST are guarantors.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Stead LF**, Perera R, Bullen C, *et al*. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008;CD000146.
2. **Mooney ME**, Leventhal AM, Hatsukami DK. Attitudes and knowledge about nicotine and nicotine replacement therapy. *Nicotine Tob Res* 2006;**8**:435–46.
3. **Hon L**. A non-smokable electronic spray cigarette (CA 2518174). (Patent notice). Canada: Canadian Patent Office Record 2005;**133**:129.

4. **Zozima K.** *Cigarettes without smoke or regulation.* New York Times June 1, 2009. <http://www.nytimes.com/2009/06/02/us/02cigarette.html> (accessed Mar 2010).
5. **Westenberger BJ.** *Evaluation of e-cigarettes.* (Technical report). Silver Spring, MD, USA: US Food and Drug Administration, 2009. <http://www.docs.google.com/viewer? a=v6q=cache;gzlfXMEYimwJ.www.fda> (accessed Mar 2010).
6. **Breland A,** Kleykamp B, Eissenberg T. Clinical laboratory evaluation of potential reduced exposure products for smokers. *Nicotine Tob Res* 2005;**8**:727–38.
7. **Shiffman S,** West R, Gilbert D. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine Tob Res* 2004;**6**:599–614.
8. **Thornley S,** McRobbie H, Lin R-B, *et al.* A single-blind, randomized crossover trial of the effects of a nicotine pouch on the relief of tobacco withdrawal symptoms and user satisfaction. *Nicotine Tob Res* 2009;**11**:715–21.
9. **MedSafe.** *Consumer medicine information: Nicorette® inhaler.* Wellington: MedSafe. 2009. <http://www.medsafe.govt.nz/profs/datasheet/n/Nicoretteinh10mg.htm> (accessed 28 Aug 2009).
10. **Demazieres A,** Luthringer R, Coppel E, *et al.* Ability of a new oral nicotine substitute to reduce smoking urge in moderate smokers. *Addict Behav* 2006;**31**:537–43.
11. **Hajek P,** Belcher M. Improved CO monitors for validating smoking abstinence by expired-air carbon monoxide levels. *Br J Addict* 1991;**86**:1029–30.
12. **Mahoney GN,** Al-Delaimy W. Measurement of nicotine in hair by reversed-phase high-performance liquid chromatography with electrochemical detection. *J Chromatogr B Biomed Sci Appl* 2001;**753**:179–87.
13. **American Psychiatric Association.** *Diagnostic and statistical manual of mental disorders fourth edition, text revision: DSM- IV-TR.* Washington, DC: American Psychiatric Association, 2000.
14. **Sayette MA,** Shiffman S, Tiffany ST, *et al.* The measurement of drug craving. *Addiction* 2000;**95**(Suppl 2):S189–210.
15. **Hajek P,** Jarvis MJ, Belcher M, *et al.* Effect of smoke-free cigarettes on 24 h cigarette withdrawal: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* 1989;**97**:99–102.
16. **Fagerström K,** Furberg H. A comparison of the Fagerström test for nicotine dependence and smoking prevalence across countries. *Addiction* 2008;**103**:841–5.
17. **Hukkanen J,** Jacob P, Benowitz N. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005;**57**:79–115.