Voke® nicotine inhaler for smoking cessation and reduction

Lead author:
Ester Ruiz Romeu
Regional Drug & Therapeutics Centre (Newcastle)
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Summary

- Nicotine replacement therapies (NRT) aim to replace nicotine from cigarettes to ease the transition from tobacco smoking to abstinence. NRT products are available in a wide range of presentations. Nicotine inhalers mimic the closest to the hand-to mouth actions of smoking, although there's no strong evidence that any single type of NRT is more effective than another. All of the commercially available forms of NRT increase the rate of long-term quitting by approximately 50% to 60% in patients who are motivated to quit.

- The use of NRT in England for smoke cessation/quitting has been overtaken by the use of E-cigarettes, with over a third of smokers using an E-cigarette in their most recent quit attempt compared with one in five using NRTs.

- NRTs and other nicotine-containing products, including E-cigarettes, that are presented for cutting down, quitting and reducing the harms of smoking are considered to be medicinal products. Manufacturers can apply for a marketing authorisation to the MHRA with a view to that product becoming prescribable.

- Voke® inhaler is the first non-electronic cigarette-like nicotine inhaler licensed and marketed as a GSL product. It is the non-electronic version of e-Voke, which is also approved, but has not been launched. Voke is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking. It is indicated for adults over 18 years of age, including pregnant women.

- Each pack contains one Voke stick device and one canister containing 9 mg nicotine, which provides approximately 20 charges of 0.45 mg of nicotine for the stick.

- No further efficacy studies were conducted, but some pharmacodynamic measures regarding cravings were included in one pharmacokinetic study. This study consisted of four parts (A-D), two assessing Voke inhaler alone (n=18, Part A, and n=18, Part C), and two assessing Voke inhaler versus the reference product, Nicorette 10 mg® Inhalator (n=24, Part B, n=24, Part D). This study did not include any evidence for effectiveness in smoking cessation (i.e. reduction of smoked cigarettes).

- Voke is a hybrid product therapeutically equivalent to the reference product Nicorette 10 mg Inhalator. There was a lack of bioequivalence between products. However, Voke pharmacokinetic profile was qualitatively closer to that of a cigarette, although with lower absolute nicotine concentrations. Also, craving relief was generally greater for Voke device than for Nicorette 10 mg Inhalator. Voke was well tolerated and its safety profile was similar to Nicorette Inhalator and consistent with other forms of NRT.

- There is a large body of literature on NRT for smoking cessation, but very limited data is available regarding the specific efficacy of nicotine inhalers. Two recent Cochrane reviews found that the form of nicotine delivery of NRTs is unrelated to effectiveness, and that evidence to date favours the use of combination versus single NRT form. There are limited studies assessing the efficacy on smoking cessation of NRTs versus E-cigarettes, as well as in particular populations, such as pregnant women.

- Voke 0.45 mg inhaler costs £8 for 1 pack, which contains 20 charges. Each charge provides comparable number of inhalation to a conventional cigarette. Cost of treatment cannot be easily compared with other NRT, since dosage differs widely between forms and most are used in combination. Price per equivalent cigarettes is likely to be more expensive than for E-cigarettes that are not licensed as medicinal products.

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Introduction and background

In the UK, 14.7% of people aged 18 years and above smoked cigarettes in 2018, which equates to around 7.2 million people in the population.[1] In England 14.4% of adults smoked,[1] and while it has fallen considerably over the last few decades, smoking remains the leading preventable cause of illness and premature death and one of the largest causes of health inequalities.[2] In 2017/18, an estimated 489,300 NHS hospital admissions in England were linked to smoking-related conditions.[1] An estimated 16% (77,800) of all deaths in 2018 were attributed to smoking.[1] In addition, in England smoking costs approximately £12.6 billion a year to society, including costs in social care, the NHS and from lost productivity.[3]]

Two-thirds of smokers say they want to quit.[3,4] However quitting tobacco use is difficult due to psychological and physiological dependence on smoking. The physiological dependence is caused by the nicotine component of tobacco.[4] Marketed cigarettes contain 6–13 mg of nicotine, of which the smoker typically absorbs 1–3 mg.[5] Nicotine is inhaled into the lungs in the form of tobacco smoke reaching the brain within 15-20 seconds.[2] However, nicotine addictiveness depends on a number of factors other than its delivery speed (e.g. other chemicals, pH, rate of absorption, dose, delivery system, environment and behaviour).[2]

Nicotine replacement therapy (NRT) aims to replace nicotine from cigarettes to ease the transition from cigarette smoking to abstinence. It works by reducing the intensity of craving and withdrawal symptoms.[4] All forms of NRT deliver nicotine much more slowly and at lower doses than smoking cigarettes, delivering peak plasma nicotine levels within about 10 minutes for the faster acting NRT products. This makes them less addictive than cigarettes.[2] However, NRT provides users with nicotine without the additional harmful elements of tobacco. This should reduce the motivation to smoke and the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking, thereby increasing the likelihood of remaining abstinent.[4]

NRTs available in the UK are as follows:[4]

- Nicotine transdermal patches (Worn over 16 hours: 5 mg, 10 mg, 15 mg, 25 mg doses. Worn over 24 hours: 7 mg, 14 mg, 20 mg, 21 mg, 30 mg doses)
- Nicotine chewing gum (2 mg and 4 mg doses)
- Nicotine sublingual tablet (microtabs 2 mg dose)
- Nicotine lozenge (1 mg, 1.5 mg, 2 mg and 4 mg doses)
- Nicotine inhalation cartridge plus mouthpiece (Cartridge containing 10 mg – *Now, also Voke 0.45mg nicotine inhaler from October 2019)*
- Nicotine metered nasal spray (0.5 mg dose/spray)
- Nicotine oral spray (1 mg dose/spray)

Among all NRT products, nicotine inhalers mimic more closely the hand-to mouth actions of smoking, and its fast-acting effects makes them useful for immediate cravings.[3,4] However, the use of NRT in England for smoke cessation/quitting has been overtaken by the use of E-cigarettes, with over a third of smokers using an E-cigarette in their most recent quit attempt compared with one in five using NRTs.[6,7] This translates to a prevalence of approximately 2.9 million adult E-cigarette users in Great Britain in 2017, while about 600,000 people were estimated to be NRT users.[2]

UK legislation

NRT products are regulated within the country's medicines regulatory framework. In the UK, medicines are regulated by the Medicines Act 1968, amended to be in line with the EU legislation. The MHRA is responsible for regulating nicotine-containing products that are medicinal products, including E-cigarettes.[8-11] Manufacturers can apply for a medicines marketing authorisation with a view to that product becoming prescribable.[11] The MHRA advice that a submission of an abbreviated dossier in relation to safety and efficacy, by using a comparative pharmacokinetic study comparing the new product to an appropriate reference medicinal product, would be sufficient. Hence, clinical efficacy trials are not needed and assessment of efficacy is based on evidence that adequate blood levels of nicotine are achieved.[8,11] Given the intended route of administration, an inhaled nicotine product such as Nicorette® Inhalator has been advised as being a suitable reference product, including for E-cigarettes marketing authorisation applications.[8]

In England, E-cigarettes are not currently available on prescription but are subject to the EU Tobacco Products Directive (TPD) and Trading Standards and can be bought online and from vape shops, pharmacies and other retail outlets, while NRT can be bought over the counter (OTC) or obtained on prescription from a licenced health professional.[6]

Guidance and related advice

NICE have produced other multiple guidelines on smoking cessation, prevention and harm reduction, some of which include recommendations on NRT use:

- PH5 Smoking: workplace interventions (Published April 2007)
- PH14 Smoking: preventing uptake in children and young people (Published November 2008)
- PH23 Smoking prevention in schools (Published February 2010)
- PH26 Smoking: stopping in pregnancy and after childbirth (Published June 2010)
- PH39 Smokeless tobacco: South Asian communities (Published September 2012)
- PH45 Smoking harm reduction (Published June 2013)
- PH48 Smoking: acute, maternity and mental health services (Published November 2013)
- NG92 Stop smoking interventions and services (Published March 2018, uptakes and replaces the guidelines on smoking, "Brief interventions and referrals" (PH1, published March 2006) and "Stop smoking services" (PH10, published February 2008).

All these guidelines, including the most recent NG92, will be updated and amalgamated in a new guideline, "Tobacco: preventing uptake, promoting quitting and treating dependence", whose expected date of publication is January 2021. Key areas in which new evidence will be reviewed include the use of NRT and E-cigarettes aimed at helping women to quit smoking if they are pregnant, planning a pregnancy or who have recently given birth; and E-cigarettes (licensed or consumer) compared with other smoking cessation or harm reduction interventions or no intervention as a means of stopping or cutting down on smoking.[12]

Public Health England (PHE) published in 2018 an evidence review of E-cigarettes and heated tobacco products, which also partially discussed the use of NRT, particularly compared to E-cigarettes. This report updated the 2015 PHE report, and

PHE will continue to update evidence base on E-cigarettes and other novel nicotine delivery systems annually until 2022.[11] The 2015 PHE report stated that since 2013 E-cigarettes had been the most common quitting aid for smokers in England. Most recent data suggests that E-cigarettes use for quitting has plateaued since 2015, and so it has for NRT OTC use.[2] Still, PHE recommends using NRT or E-cigarette as stop smoking support options, which makes it 1,5 times as likely a person to will succeed. Chances are even greater (doubled) if using a stop smoking medicine prescribed by a GP, pharmacist or other health professionals.[3]

Some recommendations and advice published in the abovementioned guidelines/reports also discuss the use of NRT in particular contexts such as adolescents, pregnant women and NRT combination use:

- The NICE NG92 guideline covers smokers over the age of 12, and it is advised to consider NRT together with behavioural support for this young population.[13] However, there are inconsistencies in the licensing for different NRT products in the UK regarding their use by young people. Some recommend that its use should be avoided in this population, and others such as Voke inhaler state a clear contraindication.[14]
- The licence for prescribing NRT was extended in the UK in 2005 to include use in pregnancy, and currently, NRT is widely prescribed to pregnant women who smoke.[2] NICE PH26 guideline recommends offering NRT to pregnant women who smoke if smoking cessation without NRT fails, or once they have stopped smoking. If pregnant women wish to receive NRT, professional judgement must be used whether to offer a prescription. Limited evidence is available about whether or not NRT is effective during pregnancy or has any impact in the child.[15]
- Regarding treatment of choice, NRT, varenicline, and bupropion hydrochloride, are effective drug treatments to aid smoking cessation.[16] There's no strong evidence that any single type of NRT is more effective than another,[17] but there is good evidence to show that using a combination of NRT is more effective than using a single product.[17] Data collected in English Stop Smoking Services from 2015-16 and 2016-17 showed that the highest number of quit attempts involved combination NRT, although with a lower quit rate compared to combined use of an E-cigarette plus a licensed medicine.[2] If a person who smoke wants to quit, NICE NG92 recommends health and social care workers in primary and community settings to explain that a combination of varenicline and behavioural support or a combination of short-acting and long-acting NRT are likely to be most effective.[13]

For further information, always refer to the summary of product characteristics for prescribing information on individual NRT preparations.

The Voke nicotine inhaler

Voke 0.45 mg inhaler is a NRT product consisting of a non-electronic nicotine inhaler for people who want to reduce, replace or stop smoking. It is a hybrid product therapeutically equivalent to the reference product Nicorette® 10 mg Inhalator (McNeil Products Limited).[14,18] Voke was first licensed by the MHRA in September 2014, and launched as a GSL product in October 2019. The electronic version (e-Voke) was licensed in November 2015, but has not yet been launched. An NTAG review was published in 2016 regarding the e-Voke cigarette for smoking cessation and reduction".[19]

Voke relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid adult smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. Voke is indicated in pregnant and lactating women making a quit attempt, and it is contraindicated in children and adolescents under the age of 18 years.[14]

One pack contains 1 Voke stick device that resembles a tobacco cigarette and 1 canister with a similar size to a pack of 20 cigarettes.[14,20] Each pack (canister) contains 9 mg nicotine, and provides approximately 20 charges of 0.45 mg of nicotine for the stick, apart from the first use which delivers less than 0.43mg). Each charge provides comparable number of inhalations (puffs) to a conventional cigarette. The breath-operated valve allows the user to self-titrate the inhalation, so the rate of nicotine delivered is dependent on an individual's depth of inhalation.[14,20]

The maximum daily dose consists of 2 packs.[14] Once opened, the whole pack needs to be discarded within 7 days. Excipients include propylene glycol, ethanol, levomenthol, HFA134a and saccharin as a sweetener agent.[14]

Evidence for the efficacy of Voke

No new non-clinical studies were conducted, and one clinical study was performed to determine the pharmacokinetics and tolerability of inhaled nicotine via the Voke device versus the reference medicine, Nicorette 10mg Inhalator. The Nicorette 10mg Inhalator was selected as the comparator because it was the closest available presentation to Voke device.[21] The application submitted to the MHRA was also supported by data from published literature on the use of inhaled nicotine for smoking cessation. In addition, it was supported by the well-established use of other approved nicotine-containing products on the market together with no new or unexpected safety concerns observed by the use of the Voke inhaler.[18]

No further efficacy studies were conducted, but some pharmacodynamic measures regarding cravings were included in the pharmacokinetic study.[18,21] The efficacy of nicotine was not further discussed in the study.[18] The study comprised 4 parts:[18,20,21]

- **Part A:** randomised, single-blind, multi-dose study to determine arterial pharmacokinetics of orally inhaled nicotine delivered via Voke nicotine inhaler at three nicotine dose levels: 0.22 mg, 0.45 mg and 0.67 mg.
- **Part B:** randomised, open-label, single-blind, three-way crossover study to determine the venous pharmacokinetics of orally inhaled nicotine at two dose levels (0.45mg and 0.67mg) delivered via the Voke nicotine inhaler device in comparison to the Nicorette Inhaler (10 mg)
- **Part C:** open-label study to determine the tolerability and venous pharmacokinetics of repeat high doses of orally inhaled nicotine delivered via the Voke nicotine inhaler device at one dose level of nicotine (0.67 mg).
- **Part D:** randomised, open-label, two-way crossover study to determine the venous pharmacokinetics of orally inhaled nicotine at the medium dose level (0.45 mg) delivered via the Voke nicotine inhaler device in comparison to the Nicorette Inhaler (10 mg)

Results from **Parts A and C**, and from **Parts B and D**, were published in two separate articles, which are discussed below.[20,21] Participants were healthy volunteers aged 18-55 years that had smoked ≥10 manufactured cigarettes per day and smoked their first cigarette within 1 h of waking, had expired carbon monoxide >10 ppm on screening and were required to abstain from smoking for 12 h prior to

their scheduled dosing time.[20,21] The primary outcome measure was the pharmacokinetic assessment of plasma nicotine.[20,21] Further information on dose(s) administration can be found in table 1.

Table 1. Dose administration via Voke and Nicorette inhalers.[5,20,21]

	Dose administration
Voke Inhaler	Single 0.22/0.45/or 0.67mg dose (1 charge) administered as: One inhalation every 15 s over ~ 2 min. (~ 8 inhalations)
Nicorette 10 mg Inhalator	Single dose 10 mg administered as: One inhalation every 15 s over ≤20 min (~ 80 inhalations). If inhaled for 20 min = ~4 mg of available nicotine Each puff delivers ~ 0.13mg of nicotine

Arterial (Part A) and venous (Part C) pharmacokinetics of orally inhaled nicotine via Voke inhaler

In **Part A** of the study (N=18), each participant was randomly assigned to one of three groups. Each group (n=6) received two single nicotine doses via the Voke inhaler, at two dose levels: 0.22 mg followed by 0.45 mg; 0.22 mg followed by 0.67 mg; and 0.45 mg followed by 0.67 mg. The two doses were separated by a washout period of 5.5 to 6.5 h, to ensure that the arterial plasma nicotine from the first dose had reached baseline concentrations before the second dose.[20] Arterial plasma concentrations of nicotine were measured over time and derived pharmacokinetics parameters were summarised separately by dose levels.[20] The mean arterial plasma concentration rose sharply following administration, with detected presence of nicotine as early as 2 minutes (first sampling time point) after the first inhalation (see table 2).[20] Pharmacokinetic parameters were essentially dose proportional with regard to the dose inhalation.[18]

Table 2. Arterial plasma pharmacokinetics (**Part A**).[20]

	Nicotine 0.22 mg	**Nicotine 0.45 mg**	**Nicotine 0.67 mg**
Nicotine concentration 2 min post-inhalation , mean (SD), ng/ml	1.1 (0.78)	2.06 (0.92)	2.59 (1.18)
C_{max}, mean (SD), ng/ml	2.11 (0.67)	3.73 (1.13)	4.38 (1.18)
T_{max}, median (range), min	10.0 (6-20)	7.0 (6-10)	6 (4-10)
AUC_{last} mean (SD), ng. min/ml	118.6 (127.3)	241.7 (152.6)	296.9 (124.6)
AUC_{all} mean (SD), ng. min/ml	145.7 (132.5)	274.4 (146.5)	334.4 (124.2)

C_{max}: maximum plasma nicotine concentration; T_{max}: time to maximum plasma nicotine concentration; AUC_{last}: area under the plasma concentration-time curve from time zero to the end of the last quantifiable concentration; AUC_{all}: area under the plasma concentration-time curve from time zero to the end of the sample collection period.

In **Part C** of the study (n=18), all participants received repeat doses of 0.67 mg of nicotine over the period of one day. One complete refill of the Voke device was inhaled every hour for 12 h, by taking one inhalation every 15 seconds until the device was empty. Venous plasma concentrations of nicotine increased steadily throughout the 12 h dosing period, reaching a steady state oscillation at later time

points, with a post-dose nicotine level as high as 10.40 (±3.68) ng/ml.[18,20] This is however considerably lower than the range of venous plasma nicotine concentration recorded after smoking a cigarette containing 1.2 mg nicotine every hour (approximately 20-50 ng/ml).[20]

Pharmocokinetics and effect on craving and smoking urges compared with Nicorette Inhalator 10 mg – Parts B and D

In **Part B** of the study (N=24), each participant was randomised to receive a single nicotine dose of 0.45 mg or 0.67 mg via Voke device, and a single dose via Nicorette 10 mg Inhalator, for three consecutive days.[21] Patients were to inhale one nicotine dose level on one day, a second dose level on a second day, both via the Voke device, and one treatment of Nicorette Inhaler 10 mg on a third day.[18] The first refill of Voke inhaler was tested in this part.[21]

In **Part D** of the study (n=24), all participants were randomised to receive one complete refill of Voke 0.45 mg nicotine inhaler one day, and one treatment of Nicorette 10 mg Inhalator on another day, for two consecutive days.[18] The fourth refill of Voke inhaler was tested in this part.[21]

In both, **Part B and D**, results with Nicorette showed higher, but later, nicotine venous plasma peak than the Voke device.[21] However, Voke provided higher amounts of nicotine within the first 10 minutes (AUC_{1-10}), confirming a higher early nicotine delivery with Voke inhaler (see table 3).[21]

Efficacy was evaluated by assessing the impact of the test devices on craving satiation and smoking urges, and their effect in aspects of nicotine withdrawal, using a visual analog scale (VAS) and the questionnaire on smoking urges (QSU-Brief) at different time points along 5 h.[21] In both **Part B and D**, mean VAS scores for craving and QSU-Brief total scores were lower for the Voke device than for Nicorette 10 mg Inhalator, indicating higher craving relief.[21] In part B, the effect on reducing craving was statistically significant greater with Voke 0.45mg than with Nicorette Inhalator 10 mg in VAS AUC (p=0.029) and QSU-Brief scores between 2-, 3- and 4- h (p≤0.05).[21] The results were similar in Part D (0.45 mg) although the difference did not reach statistical significance.[21] A greater relief of craving was also shown with Voke 0.67 mg, but statistical significant difference compared to Nicorette was achieved in less time points.[21]

Table 3. Venous plasma pharmacokinetics (**Part B and D**).[18,20,21]

	Part B (N=24)			**Part D (N=24)**	
	Nicorette Inhalator 10 mg	**Voke device 0.45 mg**	**Voke device 0.67 mg**	**Nicorette Inhalator 10 mg**	**Voke device 0.45 mg**
Nicotine concentration 2 min post-inhalation , mean (SD), ng/ml	0.73 (0.95)*	0.86 (1.05)*	1.03 (1.21)*	0.69 (0.99)*	0.84 (1.15)*
C_{max}, mean (SD), ng/ml	6.57 (2.97)	3.28 (1.24)	3.92 (1.24)	7.63 (4.72)	3.52 (1.38)
T_{max}, mean (SD), min	38 (11.8)	18.7 (8.6)	19.2 (11.8)	36.3 (12.4)	21.0 (13.5)
AUC_{last} mean (SD), ng. min/ml	977.7 (498.7)	430.8 (273.8)	545.3 (334.4)	991.5 (595.4)	406.1 (298.9)

AUC_{all} mean (SD), ng. min/ml	987.7 (487.7)	453.3 (259.0)	563 (322.9)	1002.6 (584.5)	433.2 (284.2)
AUC_{1-10} mean (SD), ng. min/ml	13.5 (9.9)	18.4 (11.3)	22.5 (13.2)	14.2 (13.8)	17.3 (13.0)

C_{max}: maximum plasma nicotine concentration; T_{max}: time to maximum plasma nicotine concentration; AUC_{last}: area under the plasma concentration-time curve from time zero to the end of the last quantifiable concentration; AUC_{all}: area under the plasma concentration-time curve from time zero to the end of the sample collection period; AUC_{0-10}: area under the plasma concentration-time curve from time 0 to 10 min.*

Clinical findings conclusions

There was a lack of bioequivalence between the novel Voke device and the Nicorette 10 mg Inhalator. Voke provided a lower total nicotine exposure (plasma nicotine AUC and C_{max}), but a faster venous nicotine delivery than Nicorette Inhalator (T_{max} of 18.7 min for Voke, 38 min for Nicorette, venous plasma concentration Part B). [18,2]

The dose and likely absorption route differences, despite both being orally administered, may explain such pharmacokinetic differences.[21] Nicorette Inhalator generates a vapour that results in predominantly oromucosal (non-pulmonary) deposition and absorption, which is consistent with an earlier venous peak and a low, delayed arterial peak.[18,20] In contrast, the faster Voke nicotine delivery might reflect a greater degree of pulmonary absorption, which is evidenced by an earlier arterial peak relative to venous levels (see limitations below).[18,20] This pharmacokinetic profile is qualitatively similar to that of a cigarette, although at lower absolute nicotine concentrations[20] and with a lower arterial/venous nicotine concentration ratio.[22] Overall, the shorter T_{max} might explain the similar –and greater at most time points- Voke effect to Nicorette Inhalator with regard to craving relief.[18,21]

In summary, based on the following points, Voke inhaler may have a greater acceptability and efficacy relative to currently available NRT products. However, this will require confirmation from randomised efficacy trials.[20]

- Voke inhaler nicotine administration is quantitatively lower than that of a cigarette, but with a similar qualitative pharmacokinetic profile.
- Voke inhaler provides higher craving reduction at most time points compared to Nicorette 10 mg Inhalator
- Voke inhaler has a cigarette-like shape, which also looks like many nicotine electronic delivering devices, but without being electronic.
- The number of provided puffs is similar to that of a cigarette, which is substantially less puffs required by the Nicorette Inhalator.

Rationale for Voke 0.45 mg dose

The rationale for selecting the 0.45 mg dose as the marketed formulation was based on the statistically superior effect on craving compared to the Nicorette 10 mg Inhaler (in Part B) as well as the arterial pharmacokinetics seen in Part A, which showed close results to those achieved by the high 0.67 mg strength.[18]

Limitations of the studies

In Parts B and D of this study, pharmacokinetic analysis were carried out using venous blood samples and some of the conclusions drawn are based on an

extrapolation of the results to the arterial pharmacokinetic profile.[20,21] Therefore, comparisons between arterial and venous peaks were made using measurements in different and independent parts of the study.

Also, the evidence used to support such hypothesis, is that Nicorette 10 mg Inhalator is not marketed anymore and the national assessment report (PL 15513/0179) could not be located. A higher strength of Nicorette inhalator, Nicorette 15 mg, is currently available. No studies comparing Voke inhaler with Nicorette 15 mg Inhalator are available, although Nicorette 15 mg showed bioequivalence to Nicorette 10mg inhalator. Nicorette 15 mg Inhalator had additionally shown efficacy outcomes compared to cigarettes use. Despite satisfaction levels were higher for cigarette smokers than with those using the Nicorette 15 mg inhalator, clinical data showed comparable craving scores between both groups and that Nicorette 15 mg Inhalator had some efficacy in reducing cigarette use in smokers.[23] To note, the use of Voke nicotine inhaler was not assessed in comparison with cigarette smokers, so direct comparison of levels of craving and satisfaction cannot be concluded.

Regarding special populations, Voke is indicated in pregnant and lactating women making a quit attempt,[14] although specific studies for this population have not been performed. In March 2019 data from the first-ever randomised clinical trial on the use of a nicotine inhaler (Nicotrol® Inhaler 10mg, US) vs placebo in pregnancy were published. It was found that smoking-cessation rates were similar for the nicotine and placebo inhaler groups, but significantly greater reduction in cigarettes/day use and fewer preterm deliveries were found in the nicotine inhaler group.[24] Overall, further research of the impact of nicotine and novel nicotine delivery systems, including E-cigarettes, are needed in pregnant women.[2]

General evidence for NRT in smoking cessation

Evidence for nicotine inhalers in smoking cessation

A recent Cochrane review published in 2019, included 63 randomised trials to determine the effectiveness and safety of different forms, deliveries, doses, durations and NRTs, for achieving long-term (≥6 months) smoking cessation, compared to one another. The primary efficacy outcome was smoking cessation. Overall only 6 of the 63 studies included the use of nicotine inhalers, alone or in combination with nicotine patches, which were included in subgroup analysis such as fast-acting NRT versus patch, type of fast-acting NRT comparisons, and combination versus single-form NRT:[4]

- **Comparison of fast-acting NRT compared to nicotine patch** found no significant difference in effect on smoking cessation between NRTs subgroups. Only 1 of the 8 studies included in this analysis assessed the use of nicotine inhaler, which only included 6/118 of fast-acting NRT users.[4]

- **Comparisons between fast-acting NRTs** were reported in one trial, which did not show statistically significant differences on smoking cessation. Only 2 subjects used nicotine inhaler in this trial.

- **Comparisons between combination versus single NRT** form favoured combination over single-type NRT for smoking cessation. Fourteen studies were included in this analysis, 3 of which compared nicotine inhalers alone or in combination with patches.[4] Caldwell 2016 and Bohadana 2000 compared

the use of nicotine inhaler plus patch versus the patch or inhaler alone, respectively.Combination therapy showed improved effects (prolonged abstinence and cessation rates, respectively). Tønnesen 2000 compared the use of nicotine inhaler (Nicorette 10 mg), nicotine patch, inhaler plus patch, and a very low dose patch. In this study, only nicotine patch maintained superiority in sustained abstainers and success rates up to 1 year. At 2 and 6 weeks, the nicotine patch and the combination of patch and inhaler were significantly more efficacious than the low dose patch. Nicotine inhaler alone was not more efficacious than the patch.

Previously, a review updated in 2018 (first published in 1996), included 133 trials to determine the effectiveness and safety of NRT for achieving long-term smoking cessation (≥6 months), compared to placebo or 'no NRT' intervention.[25] The primary outcome was smoking cessation in the intervention and control groups. Types of NRT included chewing gum, transdermal patches, nasal and oral spray, inhalators and tablets or lozenges. Subgroup analyses for each form of NRT were performed. However, there were only 5 of 133 trials studying nicotine inhalators. The author's concluded that all of the commercially available forms of NRT increase the rate of long-term quitting by approximately 50% to 60%, regardless of setting in patients who are motivated to quit. The form of delivery of NRT is unrelated to effectiveness, so other considerations such as preferences, availability, or cost might determine the form of NRT chosen.[25]

At present, none of these or other published systematic reviews or meta-analyses include Voke use alone or in combination.

Evidence for E-cigarettes vs NRT

In England, around 38% of adults who smoke and tried to stop or stopped in 2017 reported they used an E-cigarette in their recent quit attempt, compared with 20% who reported using NRT (18% OTC, and ~2% on prescription).[2] However, there are limited studies assessing the efficacy on smoking cessation/abstinence of E-cigarettes versus NRT.

An updated version of the 2014 Cochrane review "Electronic cigarettes for smoking cessation" published in 2016 did not identify any new RCTs, which were limited to two of the 24 included studies.[26] From these two, only one (Bullen 2013) compared E-cigarettes with a NRT, being the NRT a nicotine patch.[27] 657 people were randomised (289 to nicotine E-cigarettes, 295 to patches, and 73 to placebo E-cigarettes). There was no significant difference in 6-month continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine E-cigarette, patch and placebo E-cigarette arms respectively).[27] However, it had insufficient statistical power to conclude superiority of nicotine E-cigarettes to patches or to placebo E-cigarettes.[27]

A new RCT performed in the UK has been published in 2019.[28] Hajek and colleagues compared the sustained abstinence for 1 year, which was validated biochemically. A total of 886 participants underwent randomisationto a second-generation E-cigarette, (n=439) or to nicotine-replacement group (n=447). In the NRT arm, 88% of participants used NRT combinations.[28] At the target quit day, nicotine patch was used by 84% of participants, followed by nicotine inhalator (37%), mouth spray (28%), mouth strips (15%), lozenge (9%), chewing gum (8%), microtabs (8%), and nasal spray (0.5%).[28] The 1-year abstinence rate was 18.0% in the E-cigarette group, as compared with 9.9% in the NRT group (RR, 1.83; 95% CI,

1.30 to 2.58; p<0.001). Among participants with 1-year abstinence, those in the E-cigarette group were more likely than those in the NRT group to use their assigned product at 52 weeks (80% [63 of 79 participants] vs. 9% [4 of 44 participants]). The authors concluded that E-cigarettes were more effective for smoking cessation than NRT, when both products were accompanied by behavioural support.[28] However, they caution that product assignments cannot be blinded, which may have an impact on the expectation effects of participants and the effort they put into their quit attempt.[28] Sub-analyses by type of NRT were not performed.

Safety

The use of Voke was well tolerated with an adverse event (AE) profile similar to Nicorette 10 mg Inhalator.[21] Almost all subjects enrolled in the Voke 4-part study experienced a treatment emergent adverse event, although these were mild or moderate in nature and consistent with other forms of NRTs.[18] Among the most common AEs were oral paraesthesia, throat irritation, headache, and dizziness, and the most reported local AE was tingling of the mouth/lips.[20,21] It is noted that there was no significant difference between dose strengths with regard to AE profile.[18]

Excipients

The assessment of non-clinical characteristics was based on relevant literature for excipients present in Voke. Levels of ethanol, propylene glycol, saccharin and the propellant HFA-134a, were below acceptable daily intake limits established by the UK health and Safety Executive, and despite most of the evidence derived from oral studies, except for HFA-134a, inhalation toxicity was considered unlikely.[18]

Nicotine

The same alerts for accidental or intentional nicotine intoxication for nicotine inhalers apply for the Voke device.[29] Nicotine is highly toxic in high concentrations by ingestion, inhalation, intra-nasally, via eye and skin contact. The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg.[14] At recommended doses, nicotine has not been found to cause any serious adverse effects.[14] Hence, NRTs are recognised as a safe and well tolerated treatment within the recommended inhaled doses, but still high levels of nicotine exposure poses a potential poisoning risk. Serious nicotine poisoning seems normally prevented since symptoms of acute poisoning include nausea, salivation, abdominal pain or diarrhoea, which may stop users from further intake.[14] Fatal poisoning from nicotine is extremely rare, although an increase of calls to poison centres due to accidental ingestion of E-cigarette liquids have been reported.[2,30]

Cardiac disorders

The 2018 PHE review summarises that findings on short-term use of NRT in quit attempts indicate that there was no evidence on any increase in the risk of heart attack, stroke or death.

Both above-discussed Cochrane reviews assessing long-term use of NRTs, reported cardiac AEs, since they had been identified as a particular area of concern.[4] It was concluded that NRT causes non-ischaemic chest pain and palpitations in a minority of users, but there was no evidence of an excess of serious cardiac problems, even in people with established cardiac disease.[25] Authors considered that NRT is a safe medication, although it was found that most studies did not look at safety. Where studies did look at safety, very few people experienced negative effects, and there was insufficient evidence to support whether different types of methods of NRT

delivery result in more frequent cardiac AEs, SAEs or withdrawals. New studies should ensure that AEs, SAEs and withdrawals due to treatment are measured and reported.[4]

Cardiac disorders associated with the use of Voke were uncommon (palpitation, tachycardia) or very rare (reversible atrial fibrillation). Vascular disorders (flushing, hypertension) were uncommon.[14] Voke should be used with caution in patients with underlying cardiovascular disease, and only under medical supervision.[14]

Cancer potencies

The 2018 PHE review discussed the cancer potencies of emissions from tobacco smoke, and other forms of nicotine delivery products. Long-term data states that there was no evidence of a relationship between NRT and cancers.[2] Cancer potencies tend to be associated with high levels of carbonyls generated by heating/combusting the atomiser coil. One study modelled cancer risks from different smoking cessation products by using published chemical analyses of emissions and their associated inhalation.[31] In this study, lifetime cancer risks of E-cigarettes (normal power) and unheated nicotine inhaler have at least 3 and 4, respectively, lower order of magnitude than tobacco smoke. This represents a risk largely under 0.5% of the risk of smoking.[2,31]

Voke inhaler is a non-electronic device. No quantifiable carbonyls, including formaldehyde, acetaldehyde, and acrolein have been detected in Voke inhaler.[32]

Cost analysis

Voke 0.45 mg inhaler costs £8 for 1 pack, which contains 20 charges for the stick.[14]] The closest NRT products are limited to 15 mg nicotine inhalators (Nicorette and Boots NicAssist), which cost up to £28.28 per pack of 36 cartridge. It is difficult to compare cost treatment, since frequency of administration (puffs) and maximum doses differ. If used up to the recommended maximum dose, the Voke inhaler is substantially more expensive than other available inhalers, costing £16 (2 packs) vs. £5.33 (6 Nicorette 15 mg cartridges). In addition, more than one NRT may be used in combination, which would raise the cost of the treatment. Voke inhaler might be more competitively priced as compared to electronic cigarette-like devices (see table 4 below), although still more costly if compared with equivalent cigarettes.

Table 4: Example of NRTs/cig-alike E-cigarettes currently on the market.

Product	Brand/Strength	Price	Dose
Nicotine Inhalator	Voke 0.45 mg	£8.00 per pack of 20	As needed, up to max 2 pack/day (40 charges) Equivalent 20 cigarettes*
	Nicorette 15 mg	£4.87 per pack of 4 £17.78 per pack of 20 £28.28 per pack of 36	As needed, up to max 6 cartridges/day
	Boots NicAssist 15 mg	£4.87 per pack of 4 £17.78 per pack of 20	
Cig-a-like E-cigarettes	Vapour 16mg and 20mg E-cigarette (non-rechargeable)	£4.99 per 1 disposable E-cigarette (incl. VAT)	As needed. Max dose N/A. Equivalent 20 cigarettes*
	Vapour 16 mg E-cigarette (rechargeable)	£5.75 per 1 rechargeable E-cigarette (incl. VAT)	As needed. Max dose N/A. Equivalent 40 cigarettes*

	Vapour VL4 Pharma+ Tobacco 16mg E-cigarette Starter Kit	£10.99 per 1 rechargeable E-cigarette + 2 cartomisers (incl. VAT)	As needed. Max dose N/A. Equivalent 80 cigarettes*
	Nicare Rechargeable Electronic Cigarette	£12.50 per 1 rechargeable E-cigarette + 2 cartomisers (incl. VAT)	As needed. Max dose N/A. Equivalent 50 cigarettes*
Nicotine Transdermal Patch	Nicorette Invisipatch 25 mg	£11.15 per pack of 7 £18.28 per pack of 14	1 patch/day
	Nicotinell TTS 30 (21mg/24h)	£24.51 per pack of 21 £9.97 per pack of 7	
Nicotine Nasal Spray	Nicorette 10mg/ml (500 microgram/dose)	£16.18 per 10 ml pack	1 spray into each nostril as needed. max 1 spray into each nostril twice/h or 64 sprays/day.
	Boots NicAssist 10mg/ml nasal spray		
Nicotine Mouth Spray	Nicorette QuickMist 1mg/dose	£20.58 per 26.4 ml pack £13.03 per 13.2 ml pack	1 or 2 sprays as needed. Max 4 sprays/h, 64 sprays/24 h.
Nicotine Sublingual Tablet	Nicorette Microtab 2mg	£15.23 per pack of 100	1 or 2 tabs/h. Max 40 tabs/day
	Boots NicAssist 2 mg microtab		
Nicotine Gum	Nicorette 2 mg	£3.52 per pack of 25 £10.26 or £10.27 per pack of 105 £16.42 or £16.41 per pack pf 210	As needed. Max 15 daily If smoking > 20 cigarettes/day, use 4mg; ≤20 cigarettes/day, use 2mg.
	Nicorette 4 mg	£3.53 per pack of 25 £12.55 to £12.57 per pack of 105 £20.28 per pack pf 210	
	Nicotinell 2mg	£8.26 per pack of 96 £14.23 per pack of 204	As needed. Max 25 x 2 mg or 15 x 4 mg pieces/day. If smoking <20 cigarettes/day, 2 mg; 20-30 cigarettes/day, 2 mg or 4 mg; >30 cigarettes/day, 4 mg.
	Nicotinell 4mg	£10.26 per pack of 96	
Nicotine Lozenges	Nicorette Cools 2 mg	£3.34 per pack of 20 £12.05 per pack of 80	As needed. Max 15/day. If smoking ≥ 20 cigarettes/day, use 4 mg; <20 cigarettes/day, use 2 mg.
	Nicorette Cools 4 mg	£12.17 per pack of 80	
	Nicotinell 1 mg	£1.59 per pack of 12 £4.27 per pack of 36 £8.03 per pack of 72 £9.12 per pack of 96 £11.48 per pack of 144	As needed. Max 30 x 1 mg or 15 x 2 mg lozenges/day. If smoking <20 cigarettes/day, 1 mg lozenge; 20-30 cigarettes/day, 1 mg or 2

	Nicotinell 2 mg	£1.99 per pack of 12 £4.95 per pack of 36 £9.41 per pack of 72 £10.60 per pack of 96 £13.50 per pack of 144	mg; >30 cigarettes/day, 2 mg.
Oral tablets – Nicotine nicotine-receptor partial agonist Varenicline	Champix 0.5 mg	£54.60 per pack of 56	500 µg once daily for 3 days, then 500µg twice daily for 4 days, then 1mg twice daily for 11 weeks.
	Champix 1 mg	£27.30 per pack of 28	

*****in terms of timely administration/smoking sensation (not nicotine amount). Sources: eMIMs, BNF, SPC + online stores (E-cigarettes)

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