# Inhaled nicotine (MDI) for smoking cessation

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# Background nicotine MDI's

1. 1967 - First used - Herxheimer
2. 2009 Pharmacokinetic trial free-base nicotine pMDI (Cipla pharmaceuticals)
3. 2014 RCT nicotine mouthspray plus patch
4. 2016 RCT nicotine lactate pMDI plus patch

TABLE III—TUBERCULIN SENSITIVITY TO 10 T.U. IN CROHN'S DISEASE AND MATCHED CONTROLS ACCORDING TO AGE

| Age (yr.) | Group | Reaction to 10 T.U. | | Percentage of negative reactors to 10 T.U. |
|---|---|---|---|---|
| | | + | − | |
| Under 30 | Crohn's disease | 9 | 16 | 64 |
| | Controls | 12 | 13 | 52 |
| Over 30 | Crohn's disease | 30 | 16 | 35 |
| | Controls | 27 | 19 | 41 |

TABLE IV—MICROSCOPIC APPEARANCE OF CROHN'S DISEASE RELATED TO TUBERCULIN SENSITIVITY

| Granulomas | No. of patients | Reaction to 10 T.U. | |
|---|---|---|---|
| | | + | − |
| Present | 48 | 25 | 23 |
| Absent | 13 | 7 | 6 |

The influence of age is shown in table III. 30 years has been taken as a convenient dividing-line, and it can be seen that the prevalence of negative reactions is greater in the younger group of both patients and controls.

Detailed pathology reports were available for 61 patients, and table IV shows an analysis of results according to whether or not focal granulomas were reported.

## Discussion

We should like to thank the physicians and surgeons of the Central Middlesex, St. Marks, and University College Hospitals who allowed us to study their patients. J. M. H. was in receipt of a grant from the Medical Research Council.

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# CIRCULATORY EFFECTS OF NICOTINE AEROSOL INHALATIONS AND CIGARETTE SMOKING IN MAN

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MEAN CHANGES IN PULSE-RATE AND BLOOD-PRESSURE, AND ANALYSES OF VARIANCE

| — | Pulse-rate (beats per min.) | Systolic blood-pressure (mm. Hg) | Diastolic blood-pressure (mm. Hg) |
|---|---|---|---|
| *Mean changes from basal values:* | | | |
| Tobacco cigarette .. .. .. | + 9·8 | + 5·2 | + 3·2 |
| Nicotine aerosol .. .. .. | + 8·0 | + 6·7 | + 7·9 |
| Lettuce cigarette .. .. .. | + 0·3 | − 1·6 | − 0·3 |
| Control aerosol .. .. .. | − 1·1 | − 3·2 | − 1·5 |
| *Standard error of means* .. .. .. | ± *1·5* | ± *2·3* | ± *1·3* |

Cigarette smoking = nicotine MDI (100µg/puff) increased HR and BP

Since the circulatory effects of inhaling nicotine aerosol so closely match those of cigarette smoking, the use of nicotine aerosol as a substitute deserves investigation. It might be particularly useful in patients with respiratory disease who have difficulty in giving up cigarettes.

Original Investigation

# A pilot study of nicotine delivery to smokers from a metered-dose inhaler

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## Abstract

**Introduction:** The present study generated preliminary data on the acceptability and pharmacokinetics of nicotine administered by a simple metered-dose inhaler (MDI).

**Methods:** We conducted a nonrandomized, open-label crossover trial of 10 current smokers. On Day 1, a single cigarette was smoked *ad libitum*. On Day 2, participants took 10 puffs (20 inhalations) of 50 μg nicotine/puff through the inhaler, and on Day 3, they took 10 puffs (20 inhalations) of 100 μg nicotine/puff, each over 5 min. Nicotine pharmacokinetics, changes in heart rate and blood pressure, and the acceptability of the inhalers were measured and recorded.

tobacco-related disease and mortality in people whose tobacco addictions are resistant to current NRT and smoking cessation products. Current forms of NRT were designed to reduce the symptoms of nicotine withdrawal while limiting their addictiveness by providing nicotine at a lower dose and taking longer to achieve a maximum plasma concentration than cigarette smoking. These NRTs are used widely, and systematic reviews show them to be effective in reducing nicotine withdrawal symptoms and increasing short-term quit rates compared with placebo (Silagy, Lancaster, Stead, Mant, & Fowler, 2004). However, long-term quit rates are much lower after a single treatment with these products, and multiple treatments are usually required (Etter & Stapleton, 2006). Quit rates may be enhanced if relapsed quitters can be offered novel NRTs as a second-line or third-line treatment.

Inhalers made by Cipla – 50 and 100µg/puff

10 subjects 3 days (1) Cigarette; (2) 10 puffs 50µg; (3) 10 puffs 100µg over 10 minutes

## Table 2. Bioavailability of the inhalers relative to cigarettes

| Form | Total dose (mg) | Median relative bioavailability (interquartile range) |
|---|---|---|
| Cigarette | 1.1 | 1 |
| Inhaler: 50 μg | 0.5 | 0.429 (0.179–0.589) |
| Inhaler: 100 μg | 1.0 | 0.389 (0.353–0.563) |

# Lessons

- Bioavailability ~ 1/3$^{rd}$ cigarette
- Nicotine free base aversive
- Most subjects felt MDI would be helpful

- Less aversive nicotine – lactate salt
- Use patch for base level nicotine
- Develop RCT

# Nicotine inhaler

- Standard MDI technology
- Filled on contract in Auckland
- Nicotine lactate; anhydrous ethanol; menthol; HFA 134a
- Hand filled
- 100 and 200µg nicotine lactate/puff

# Nicotine inhaler RCT

Recruitment through advertisement
Registration via web

Inclusion: Smokers ≥ 9 cigarettes/day;  FTND ≥ 3;
Exclusion : asthmatics using ICS

502 subjects randomised
Nicotine MDI + nicotine patch vs Placebo MDI + nicotine patch

| Table 2: Abstinence outcomes† | | | | |
|---|---|---|---|---|
| | Active (n=246) | Control (n=256) | Odds Ratio (95% CI) | p |
| **Not smoked on 7 consecutive days*** | | | | |
| 1 month | 112 (45·53%) | 89 (34·77%) | 1·57 (1·10-2·25) | 0·014 |
| 1 month biochemically verified | 82 (33.33%) | 58 (22.66%) | 1.71 (1.15-2.54) | 0.008 |
| 3 month | 94 (38·21%) | 73 (28·52%) | 1·55 (1·07-2·26) | 0·022 |
| 6 month | 91 (36·99%) | 61 (23·83%) | 1·88 (1·28-2·77) | 0·001 |
| Prolonged 6 month | 78 (31·71%) | 46 (17·97%) | 2·12 (1·40-3·23) | <0·001 |
| Prolonged 6 month biochemically verified (at 1 month) | 64 (26.02%) | 36 (14.06%) | 2.15 (1.37-3.41) | <0·001 |

Abstinence not smoked on seven consecutive days
6 month prolonged abstinence with inhaler

31.7% vs. 18.0%

Odds ratio 2.12 95%CI 1.40-3.23 p<.001

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6 month prolonged abstinence with nicotine mouthspray

15.5% vs. 10.6%

Odds ratio 1.55 95%CI 1.13–2.12 p=.006

Abstinence not smoked on seven consecutive days
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6 month prolonged abstinence with nicotine mouthspray

**15.5%** vs. 10.6%

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# Nicotine inhaler

Well tolerated

Coughing

- Common initially
- Resolved quickly

How to make inhaler widely available?

- No intellectual property – anyone can manufacture
  1. Cheap
  2. But no profit motive for investors

# Conclusion

Rapid delivery of nicotine via MDI  is more effective

Inhaler has advantages over electronic cigarettes

1. Less appealing to youth
2. Tamper proof
3. No modelling of smoking behaviour
4. No heating so no creation of toxics
5. No refilling
6. No battery

Investment required to make inhaler available

Nicotine by MDI more appropriate for cessation than social e-cigarette

# NEXTs:

- Found investor (AUS) (socially motivated)
- Formed company (Quitta)
- Found approved manufacturer

- To proceed:
- Web available in US?
- Register in NZ
- E- cig alternative versus registered pharma product

# Further development

- Improve long term stability
- Manufacture automated line
- Small run hand-filled for comparison using previous production protocol
- Particle sizing nicotine output
- Medsafe approval

# Implications

1. Inhaled nicotine as part of a cessation trial improves cessation
2. Supports role for inhaled nicotine in smoking cessation

# Bioavailability old vs new

- Trials company - Zenith
- Single dose randomised crossover study old vs new inhaler
- 28 subjects
- 5 puffs 200µg/puff over 2 min
- Plasma nicotine at intervals to 8 hours
- AUC of New within 90% CI of Old ??

# Next

- Confirm bridging pK study acceptable to Medsafe for registration
- Obtain funds
- Commission study
- Proceed to develop registration dossier

**Table 1. Median maximal concentrations minus baseline levels (*C*max), concentration at 1 min ($C_{T=1}$), time to maximum concentration (*T*max), and area under the concentration curve (AUC), with interquartile ranges for the three treatment days**

| | Cigarette | Inhaler: 50 μg/puff | Inhaler: 100 μg/puff |
|---|---|---|---|
| *C*max (ng/ml) | 25.9 (13.7–55.3) | 12.5 (7.9–14.3) | 9.4 (7.5–12.1) |
| $C_{T=1}$ | 25.0 (11.3–43.7) | 4.0 (2.3–5.7) | 6.4 (4.2–9.8) |
| *T*max (min) | 2 (1–5) | 6 (5–7) | 5 (3–7) |
| AUC | 1,032.5 (572.8–1259.3) | 201.5 (84–337) | 365 (184–645) |

# Zonnic mouthspray

Zonnic is faster than gum: 15 minutes versus 46 minutes

1,423 subjects

Abstinence: not smoked on seven consecutive days

6 month prolonged abstinence

15.5% vs. 10.6%

Odds ratio 1.55 95%CI 1.13–2.12 p=.006

12 month prolonged abstinence

10.1% vs. 7.1%

Odds ratio 1.47 95%CI 1.01–2.15 p=.045

# Possibilities 2

- Register nicotine MDI as a medicine for smoking cessation
  - Regulatory issues (regulatory consultant)
    - Comparability of new MDI with old
      - Assuming similar dose/puff (100 and 200µg/puff)
      - Assuming similar particle size distribution
    - Non GCP trial (updates to protocol only to HDEC) signatures on trial documents;
    - None of these had any impact on trial outcomes.
    - *Similar mdi product licenced in UK made by BAT without efficacy trial*

# Possibilities 3

- New self funding therapeutic trial
- Others???

# Most of all we need to

- Manufacture large volume, and
- Need confidence that product can be used
-

# More rapid delivery to match smoking

| | **Cigarettes** | **NRT** |
|---|---|---|
| **Speed to brain** | 6 seconds | > 7 minutes |
| **Dose to brain** | +++++ | ++ |
| Reward | +++++ | +? |
| Dose to body | + | ++ |
| Side-effects | - | ++++ |

# Rationale of Research

Smoking - biggest cause of preventable mortality

Nicotine - primary cause of smoking addiction

Smoking - a chemical addiction, requires a chemical treatment.

NRT - safe nicotine without pyrolysis products

NRT doubles 12 month quit rates, but only 10% quit

More effective NRT is needed

# Background nicotine MDI's

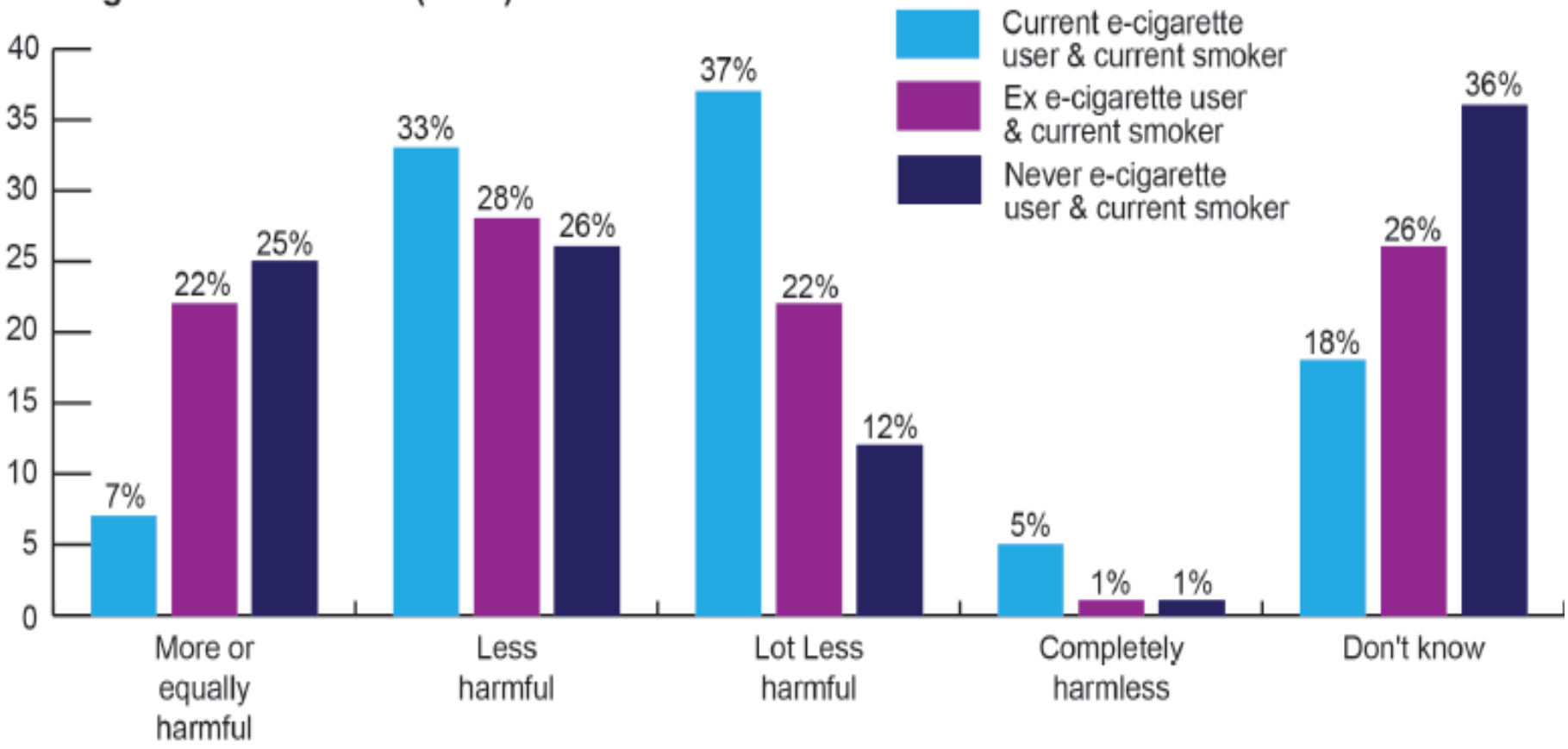
1. 1967 - First used - Herxheimer
2. 1982 - Made first nicotine MDI 1982 – Mirimar fly spray factory (12 months before CFC protocols)
    1. Took to AB Leo (Sweden) "*Great idea but regulatory authorities would never agree*"
3. 2009 Pharmacokinetic trial free-base nicotine pMDI
    1. Cipla pharmaceuticals
4. 2014 RCT nicotine mouthspray plus patch
5. 2016 RCT nicotine lactate pMDI plus patch

# We need to do:

- Improve stability (shelf life)
  - Reduce water all anhydrous ingredients
  - Closed filling no residual air in canister

- Bridging study
- Particle sizing nicotine output hand-filled vs commercial line.

**Figure 7: Perception of harms from electronic cigarettes relative to smoking among current smokers (2016)**




Unweighted base: GB adult current e-cigarette user and current smoker (n=330), GB adult ex e-cigarette user & current smoker (n=703), GB adult never e-cigarette user and current smoker (n=606)