Do very low nicotine content cigarettes and electronic cigarettes have the potential to end tobacco smoking?

Oliver Knight-West
Brigid O’Brien, Chris Bullen, Natalie Walker
Smoking prevalence in NZ

Ikeda et al. Tobacco Control (September 26, 2013)
How do we increase cessation?

• Getting rid of tobacco is unlikely, so:
  • Increase the price of cigarettes
  • Reduce nicotine content to very low levels
  • Make safer sources of inhaled nicotine more attractive, accessible, and cheap

Laugesen 2010.
Can we make cigs less addictive?

85% of smokers in New Zealand want the addictiveness of cigarettes reduced Edwards 2009

Reduced nicotine content cigarettes

- Quest 1,2,3 (Vector)
  - Nicotine yield: 0.6, 0.3, ≤ 0.05 mg cigarette
  - Nicotine content: 8.9, 5.1, 1.0 mg cigarette
  - Tar = 10 mg

- 22nd Century research cigarettes
  - Various nicotine and tar levels

Very low nicotine content (VLNC) cigarettes

- Content: ≤ 2.0 mg cigarette, Yield: ≤ 0.05 mg cigarette
Very low nicotine content cigs

• Levels of nicotine so low as to have negligible or no central effects

• Provide behavioural and sensory replacement

• Divorcing the pairing of behavioural and sensory components of smoking with rapid nicotine delivery may disrupt the reinforcing effect of smoking and assist in smoking cessation

• Such a process may be enhanced if withdrawal symptoms are managed with medications.
Is it just nicotine?

- Sensory and behavioural cues (e.g. the effects of smoke in the mouth and throat, and the action of puffing on a cigarette) become secondary reinforcers (Przulj et al. 2012)

- Other chemicals in tobacco smoke may enhance nicotine effects (Berlin & Anthenelli 2001; Talhout et al. 2007)
In smokers motivated to quit

• Nine RCTs of VLNC cigs (n = 35 – 1410)
  • Smaller studies found mixed effects on short-term abstinence; all under-powered
  • Adding NRT increased quit rates
  • One large study found an increase in 6-month self-reported continuous abstinence rates in smokers receiving standard Quitline treatment (23% vs. 15%, RR= 1.50, p< 0.001) (Walker 2012)

• VLNC cigs have also been shown to:
  • Be satisfying at least over the initial few days of abstinence from smoking (Pickworth 1999; Rose 2000; Donny 2007)
  • Reduce withdrawal symptoms, including urges to smoke and low mood (Rose 2000; Donny 2009; Barrett 2010; Perkins 2010)
  • Lead to minimal compensatory smoking (Benowitz 2012)
  • Reduce self-reported levels of dependence (Hatsukami 2010)
  • Can delay relapse back to smoking (Walker 2012)
In smokers unmotivated to quit

- **US trial of 30 adult smokers who smoked ≥20 cpd**
  - Quest 1 and 3 cigarettes over 11 days.
  - Repeated exposure to Quest 3 led to “a gradual and incomplete reduction in the number cigarettes smoked and in the motivation to smoke” and suppressed cravings. Donny 2006

- **Larger trials are now being planned in the US**
  - 22nd Century research cigarettes
    [Professor Dorothy Hatsukami, University of Minnesota, USA].
Questions for New Zealand

What would smokers do if VLNC cigarettes were available on the market at a cheaper price than regular cigarettes?

Implement a nicotine tax:
• Cigarettes with more nicotine in them have a higher excise tax than those with low nicotine
• Excise tax based on a ‘nicotine per mg’ formula.
• Nicotine content regularly tested
• Over time
  – Increase the excise tax on higher nicotine cigarettes
  – Remove the higher nicotine content brands

Benowitz 2013
Laugesen 2012
Compared to smokers who smoke regular cigarettes, will smokers offered cheaper VLNC cigarettes:

- reduce the number of regular cigarettes they smoke?
- what will the mix of regular and VLNC cigarettes look like?
- make more quit attempts, or be more likely to quit?
- have reduced measures of addiction?
- like the concept of a nicotine reduction strategy?
Trial design

• Feasibility study, single-blind, n=33
  • No intentions of quitting in the next three months
  • ≥ 18 years, Daily smokers
  • First cigarette within 30 minutes of waking

• Intervention
  • Provided with 12 weeks supply of **free** VLNC cigarettes, thus creating a large price differential. NO behavioural support

• Control
  • Free to purchase their regular brand cigarettes as per normal over a 12 week period. NO behavioural support
Dual use of regular and VLNC cigarettes

Weeks since randomisation

Average number of cigarettes smoked per day over the previous week

Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 9, Week 12

Intervention - VLNC
Intervention - Regular
Intervention - Total
Control
# Dependence and quitting

## Table of Results

<table>
<thead>
<tr>
<th>Metric</th>
<th>VLNC</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td># for whom time to first cig after waking increased to more than 30 mins</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Mean change in AUTOS score (SD)</td>
<td>-5.53 (5.55)</td>
<td>-2 (4.51)</td>
</tr>
<tr>
<td>Mean change in GN-SBQ score (SD)</td>
<td>-5.29 (4.89)</td>
<td>-1.71 (3.52)</td>
</tr>
<tr>
<td># Quit attempts</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td># Quit (abstinent last 7 days of study)</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Views on nicotine reduction

If cigarettes that were truly low in nicotine were on the market, would you be more likely to buy them instead of your regular brand, if they were….

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same price</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1 cheaper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10 cheaper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Interim conclusions

• Given the option to obtain VLNC cigs at much lower cost than regular ones could result in:
  • Dual use, some quitting, and little reduction in harm.

• Throwing NRT into the mix may result in greater levels of quitting and harm reduction, but:
  • Current NRT is overwhelmingly unpopular with most smokers
  • It is under-used, incorrectly used, and far less accessible than regular cigarettes
We need alternative, safe, sources of nicotine which:

- Address the behavioural aspects of smoking
- Have a nicotine delivery profile that matches that of regular cigarettes
- Are made widely available and cheap
- Are endorsed by medical professionals as safer alternatives to tobacco smoking

- In this scenario, would we need VLNC cigs?
Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy

Remove regular tobacco completely, i.e., only VLNC cigarettes on the market.
E-cigarettes

• Early models were unreliable and delivered nicotine in a low, slow, and inconsistent way

• Next gen products are much better, but still have some way to go before they match regular cigarettes

• Innovation has been rapid, but future evolution may be stifled depending on forthcoming regulatory frameworks

• Has NZ got it wrong at the moment?
Safety of e-cigs

- Propylene glycol safe, but long term effects of inhalation unknown
- Where toxicants found in tobacco smoke have been detected, they were at levels 9-450 times lower (and generally similar to NRT)
- Adverse events similar to NRT
- Second-hand vaping causes very minor exposure at levels that would not present health risks
- Long-term safety data years away. Any risks almost certainly to be lower than from smoking
### Registered unpublished trials

<table>
<thead>
<tr>
<th>Study Pop</th>
<th>Gartner (Australia)</th>
<th>Arouni (USA)</th>
<th>Hajek (UK, Spain, Czech Rep)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Varying motivation to quit</td>
<td>Motivated to quit</td>
<td>Motivated to quit</td>
</tr>
<tr>
<td>Product</td>
<td>18.6 mg nicotine Vype Red</td>
<td>STAM CE4 eGo Clearmizer</td>
<td>Gamucci</td>
</tr>
<tr>
<td>Sample size</td>
<td>1600</td>
<td>240</td>
<td>220, 3 centres</td>
</tr>
</tbody>
</table>
| Intervention               | • NRT choice for short term use  
• NRT choice for short and/or long term use  
• Choice of NRT and ‘cigarette like’ nicotine products for short and/or long term use | e-cig (strength unknown) Vs. 2 and 4 mg NRT gum | Standard care plus e-cig Vs. Standard care (NRT plus behavioural support) |
| Intervention period        | 3 weeks free, 6 weeks discounted | ? 12 weeks | 4 weeks |
| Follow-up                  | 12 months           | 12 weeks     | 24 weeks |
| Power                      | 80%                 | ?            | N/A [Pilot Study] |
| Primary outcome            | Self-reported 12 month continuous abstinence | Verified 12 week continuous abstinence? | Verified 4 week continuous abstinence |
## Registered unpublished trials

<table>
<thead>
<tr>
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<th>Vaughan (USA)</th>
<th>Beebe (USA)</th>
<th>Cipolla (Italy)</th>
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</thead>
<tbody>
<tr>
<td><strong>Study Pop</strong></td>
<td>Motivated to quit, 18-60 year olds</td>
<td>Females 18-65 with gynae cancer or precursors, motivated to quit</td>
<td>&gt;=18 yrs, patients with cancer diagnoses or recent MI, motivated to quit</td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td>V2 with 24mg cartridges</td>
<td>Blu Cig, dose not specified</td>
<td>T-FUMOTM</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>40</td>
<td>30</td>
<td>126</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>E-cig 24 mg nicotine Vs. Nicotrol inhaler 10 mg</td>
<td>E-cig ?nic content Vs. patches</td>
<td>E-cig 0mg nicotine plus counselling Vs. Counselling</td>
</tr>
<tr>
<td><strong>Intervention period</strong></td>
<td>4 weeks</td>
<td>6 weeks</td>
<td>?8 weeks</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>4 weeks</td>
<td>12 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>1 day point prevalence at 4 weeks</td>
<td>Point prevalence abstinence at 7 and 30 days</td>
<td>CPD 8 weeks after diagnosis or event</td>
</tr>
</tbody>
</table>
Final thoughts

With limited ability to remove tobacco from the market completely, there is merit in allowing only VLNC cigarettes to be sold, while at the same time offering clean sources of nicotine:

• particularly in forms that mimic the behavioural aspects of smoking, such as e-cigarettes.