Reductions in the nicotine content of cigarettes as a means to improving public health

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Why do people smoke?
Why do people smoke?

*People smoke for the nicotine...*

-M.A. Russell, 1976
Why do people smoke?

...but they die from the tar

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People smoke for the nicotine...

...but they die from the tar

-M.A. Russell, 1976
Framework Convention on Tobacco Control

• World’s first public health treaty
• 180 countries party to the treaty, including New Zealand
• Targets reducing both supply (Articles 15-17) and demand (Articles 6-14) for tobacco
  • Regulation of the content of tobacco products (Article 9)
Family Smoking Prevention and Tobacco Control Act

- Brought tobacco under FDA authority
- Enables the FDA to establish product standards
  - Nicotine explicitly raised as potential target
  - Must consider the risks and benefits to the population as a whole including users and nonusers
Would a product standard requiring very low nicotine levels reduce cigarette use and improve public health?
Two sources of data for today

Clinical trials

Rat self-administration
1988

The Health Consequences Of Smoking
NICOTINE ADDICTION
a report of the Surgeon General
1988

1994

DAVID KESSLER
A QUESTION OF INTENT

1998

Tobacco Control 1998;7:281–293

FROM THE AMERICAN MEDICAL ASSOCIATION

Reducing the addictiveness of cigarettes

Jack E Henningfield, Neal L Benowitz, John Slade, Thomas P Houston, Ronald M Davis, and Scott D Deitchman, for the Council on Scientific Affairs, American Medical Association
• Purpose: To determine how use of cigarettes varying in nicotine content impacts smoking and a wide range of secondary outcomes in a large study of smokers not currently interested in quitting.
Donny et al., 2015

- 840 daily smokers
  - 18+ years old
  - 5+ CPD
  - Use other tobacco products fewer than 10 days in past 30
  - Not planning to quit in next 30 days

- 10 U.S. sites
<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>AA</th>
</tr>
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Donny et al., 2015
Donny et al., 2015

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<th>AA</th>
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</table>

Study cigarettes provided free of charge

*Menthol matched*

*Double blind*
<table>
<thead>
<tr>
<th>GROUPS (7 total)</th>
<th>Nicotine Content (mg/g)</th>
<th>Nicotine Yield (ISO) (mg/cig)</th>
<th>Tar Yield (ISO) (mg/cig)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Usual brand</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
</tr>
<tr>
<td>2. Normal Nicotine</td>
<td>15.8</td>
<td>~0.73</td>
<td>~10</td>
</tr>
<tr>
<td>3. Reduced Nicotine</td>
<td>5.2</td>
<td>~0.24</td>
<td>~9</td>
</tr>
<tr>
<td>4. Very Low Nicotine</td>
<td>2.4</td>
<td>~0.11</td>
<td>~9</td>
</tr>
<tr>
<td>5. Very Low Nicotine</td>
<td>1.3</td>
<td>~0.06</td>
<td>~8</td>
</tr>
<tr>
<td>6/7. Very Low Nicotine</td>
<td>0.4</td>
<td>~0.03</td>
<td>~9 (or 13)</td>
</tr>
</tbody>
</table>

Donny et al., 2015
<table>
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<tr>
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Donny et al., 2015

30 day Follow-up
Does nicotine reduction lead to reduced smoking?
Cigarettes per day

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Cigarettes per day

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Cigarettes per day

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Cigarettes per day

![Graph showing the change in total cigarettes per day over time for different nicotine levels. The graph includes data points for UB, 15.8 mg/g, 5.2 mg/g, 2.4 mg/g, 1.3 mg/g, 0.4 mg/g, and 0.4 mg/g (HT). The x-axis represents weeks from baseline to week 6, and the y-axis represents total cigarettes per day.](image-url)
Cigarettes per day

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Cigarettes per day

*indicates significant (p<.0125) difference compared to 15.8 mg/g (controlling for BL)

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Cigarettes per day at $6/pack

*indicates significant (p<.0125) difference compared to 15.8 mg/g (controlling for BL)

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Predicted future smoking

Starting today, if the study cigarette was the only type of cigarette available to purchase, by a year from now I would...
Take home point

Low nicotine content cigarettes reduce smoking relative to normal nicotine cigarettes

Donny et al., 2007

Hatsukami et al., 2010
Does nicotine reduction lead to decreases in nicotine exposure?
Biomarkers of exposure

*indicates significant (p<.0125) difference compared to 15.8 mg/g (controlling for BL)

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Content vs. Exposure

Nicotine content

GROUPS (7 total)
1. Usual brand
2. Normal Nicotine
3. Reduced Nicotine
4. Very Low Nicotine
5. Very Low Nicotine
6/7. Very Low Nicotine

Nicotine exposure

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Hotel study

- 24 participants smoked only 0.4 mg/g SPECTRUM while residing at a hotel for 4 nights.
- Nicotine exposure decreased by at least 92-94%

Denlinger et al., Tobacco Regulatory Science, in press
Non-adherence in clinical trials

- We estimate ~25% of participants in the 0.4 mg/g groups are completely compliant, although over 60% reduce their nicotine exposure by at least 25%

- Why?
  - Partly because of the quality of the cigarettes and/or brand switching (i.e., not a nicotine effect)
  - Partly related to nicotine reduction
Take home point

Low nicotine content cigarettes reduce nicotine exposure, but people seek out other sources of nicotine.

**Walker et al., 2015**

Even when VLNC cigs were free, smokers chose to buy usual brand cigarettes (~50%)

**Hatsukami et al (under review)**

VLNC cigarettes increased the use of non-combusted tobacco products (primarily e-cigs)

**Benowitz et al., 2015**
Does nicotine reduction reduce dependence and/or lead to quitting?
Dependence

*indicates significant (p<.0125) difference compared to 15.8 mg/g (controlling for BL)

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Dependence

*indicates significant (p<.0125) difference compared to 15.8 mg/g (controlling for BL)

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Quit attempts

*indicates significant (p<.0125) difference compared to 15.8 mg/g

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Take home point

*Low nicotine content cigarettes reduce nicotine dependence and increase the likelihood that smokers will try to quit*

Hatsukami et al., 2010

**VLNC cigarettes increase**
- Quit contemplation (Benowitz et al., 2012)
- Quit attempts (Walker et al., 2015)
- Quit success (Becker et al., 2008; Walker et al., 2012)
Would nicotine reduction reduce the uptake of smoking?
Rat self-administration

Sprague-Dawley rats
1-hr daily self-administration sessions
Respond for intravenous (i.v.) infusions of nicotine
Initiation of self-administration

Smith et al., 2014 *Exp & Clinical Psychopharm*
Initiation of self-administration

Adolescents (male or female) fail to acquire at 10 μg/kg or lower

Schassburger et al., in press
Take home point

Reducing nicotine may decrease the likelihood of progressing to regular use

“Without nicotine... there would be no smoking”
Philip Morris scientist William Dunn, 1972
Concerns and critiques
Smokers will compensate for the reduction in nicotine and smoke more not less
Compensatory smoking

Light cigarettes have reduced nicotine yield. VLNC cigarettes actually contain less nicotine. The content of the tobacco is the same. With light cigarettes, smokers can and do compensate. It would be very difficult for smokers to adjust their behavior to maintain nicotine levels.
Compensatory smoking

*indicates significant (p<.0125) difference compared to 15.8 mg/g (controlling for BL)

Donny E.C. et al., 2015, NEJM, 373, 1340-9
Take home point

Minimal evidence of compensatory smoking

Other studies also fail to find evidence of lasting compensation (Benowitz et al. 2012; Hatsukami et al., 2010, 2013, 2015; Donny and Jones, 2009; Hammond and O’Connor, 2014)
Nicotine reduction will lead to potentially harmful unintended consequences?
Unintended consequences

- Withdrawal – mild throughout and unrelated to cigarette condition (Donny et al., 2015)
- Depression – no significant differences in mean CESD or % exceeding 16 (common clinical criteria) (Tidey et al., under review)
- Weight – average gain of 1.2 kg in participants assigned to VLNC cigs with TNE <6.4 nmol/ml (Rupprecht et al., in prep)
- Alcohol/marijuana use – largely unrelated to cig condition (Dermody et al., 2016; Pacek et al. in prep)
- Cognitive function – not related to cig condition (Vandrey et al., in prep)
- Adverse Events – not related to cig condition (Donny et al., 2015)
- Platelet activation – not related to cig condition (Benowitz et al., in prep)
Take home point

Little evidence of unintended medical, psychological or behavioral adverse consequences

Other trials in which participants used VLNC cigarettes for >14 days have failed to find evidence of significant negative consequences

- Benowitz et al., 2012
- Hatsukami et al., 2010
- Hatsukami et al., 2013

Caveat: non-compliance may mask unintended consequences
Smokers will perceive VLNC cigarettes as safer
Risk perception

![Perceived Lung Cancer Risk by Tx Group](image_url)
Risk perception

Perceived Lung Cancer Risk by Perceived Nicotine Content

- Perceived Nicotine Level at Week 6
  - Low/Very Low
  - Normal/High

Risk perception analysis showing the perceived lung cancer risk at Week 6.
Risk perception

![Graph showing mean risk ratings for various health risks associated with different types of cigarettes.](chart.png)

- Overall Health Risk
- Lung Cancer Risk
- Heart Disease Risk
- Stroke Risk
- Emphysema Risk
- Other Cancers Risk
- Chronic Bronchitis Risk
- Addiction Risk

Legend:
- Usual Brand Cigarette
- "Very Low" Nicotine Cigarette
- "Average" Nicotine Cigarette
Take home point

*Risk perception is affected by perceived nicotine content*
Take home point

Risk perception is affected by perceived nicotine content

... but lower risk perception may not offset the predicted gains

Data for only those reporting lower risk relative to UB
Smoker will revolt
Acceptability

Would you support or oppose a law that reduced the amount of nicotine to make cigarettes less addictive?

Data collected after 6 week of use

Rated cigarettes as low or very low in nicotine
**Take home point**

*Regulation is acceptable to both non-smokers and smokers*

<table>
<thead>
<tr>
<th>Study</th>
<th>Details</th>
<th>Support/Oppose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fix et al., 2011 (US smokers; 10+ CPD)</strong></td>
<td>If nicotine was made easily available in non-cigarette form, would you support or oppose a law that reduced the amount of nicotine in cigarettes, to make cigarettes less addictive?</td>
<td><strong>SUPPORT: 68% vs. OPPOSE: 28%</strong></td>
</tr>
<tr>
<td><strong>Connolly et al., 2012 (US)</strong></td>
<td>Do you think that the FDA should reduce nicotine in cigarettes if it would cause fewer kids to become addicted or hooked on smoking?</td>
<td><strong>SUPPORT: Non-smokers: 81%; Smokers: 74%</strong></td>
</tr>
<tr>
<td><strong>Pearson et al., 2013 (US)</strong></td>
<td>The government should reduce the amount of nicotine in cigarettes to help smokers quit.</td>
<td><strong>SUPPORT: ~50% vs. OPPOSE ~ 16% (Smokers and non-smokers)</strong></td>
</tr>
<tr>
<td><strong>Li et al., 2016 (NZ survey; N=2594)</strong></td>
<td>The nicotine content of cigarettes should be reduced to very low levels so that they are less addictive.</td>
<td><strong>AGREE/STRONGLY AGREE: 80.7% (Current smokers: 62.9%)</strong></td>
</tr>
</tbody>
</table>
We need more data
We need more data

What important questions remain?

<table>
<thead>
<tr>
<th>PI(s)</th>
<th>Clinical Trial #</th>
<th>Purpose (derived from clinicaltrials.gov)</th>
<th>Sample size</th>
<th>Estimated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatsukami</td>
<td>NCT02139930</td>
<td>To compare two different approaches to reducing levels of nicotine in cigarettes: an immediate reduction in nicotine content in cigarettes vs. a gradual reduction in nicotine content in cigarettes.</td>
<td>1250</td>
<td>August, 2016</td>
</tr>
<tr>
<td>Donny</td>
<td>NCT02301325</td>
<td>To evaluate the impact of very low nicotine content cigarettes with and without transdermal nicotine.</td>
<td>240</td>
<td>December 2016</td>
</tr>
<tr>
<td>Tidey</td>
<td>NCT02019459</td>
<td>To examine whether reducing the nicotine content of cigarettes to non-addicting levels is a viable method of reducing smoking in smokers with schizophrenia.</td>
<td>80</td>
<td>August 2018</td>
</tr>
<tr>
<td>Tidey</td>
<td>NCT02232737</td>
<td>To examine the impact of extended exposure to cigarettes varying in nicotine content to people with current affective disorders.</td>
<td>405</td>
<td>August 2019</td>
</tr>
<tr>
<td>Stitzer</td>
<td>NCT02250664</td>
<td>To examine the impact of extended exposure to cigarettes varying in nicotine content among opioid abusers.</td>
<td>405</td>
<td>August 2019</td>
</tr>
<tr>
<td>Higgins &amp; Heil</td>
<td>NCT02250534</td>
<td>To examine the impact of extended exposure to cigarettes varying in nicotine content among disadvantaged women.</td>
<td>405</td>
<td>August 2019</td>
</tr>
<tr>
<td>Shiffman</td>
<td>NCT02228824</td>
<td>To investigate the impact of different nicotine levels in cigarettes among non-daily smokers.</td>
<td>455</td>
<td>June 2016</td>
</tr>
<tr>
<td>Foulds &amp; Evins</td>
<td>NCT01928758</td>
<td>To evaluate the effect of progressive nicotine reduction in cigarettes on smoking behavior, toxin exposure and psychiatric symptoms in smokers with comorbid mood and/or anxiety disorders.</td>
<td>280</td>
<td>October 2018</td>
</tr>
<tr>
<td>Muscat &amp; Horn</td>
<td>NCT01928719</td>
<td>To address the question of whether progressively lowering nicotine content in cigarettes can reduce or eliminate nicotine dependence in smokers of low socioeconomic status.</td>
<td>400</td>
<td>October 2018</td>
</tr>
<tr>
<td>Richie</td>
<td>NCT02415270</td>
<td>To determine the short term effects of switching to tobacco products that deliver low levels of nicotine or reactive oxygen/nitrogen species (ROS/RNS) on smoking behavior and biomarkers of tobacco smoke exposure and oxidative stress.</td>
<td>70</td>
<td>May 2017</td>
</tr>
<tr>
<td>Kollins &amp; McClernon</td>
<td>NCT02599571</td>
<td>To investigate the impact of different nicotine levels in cigarettes with individuals who have ADHD.</td>
<td>350</td>
<td>March 2020</td>
</tr>
<tr>
<td>Oncken &amp; Dornelas</td>
<td>NCT02592772</td>
<td>To examine the potential effect of reducing nicotine content or menthol or both in men. It will also examine whether there are gender differences in manipulating tobacco flavors and nicotine concentrations in cigarettes on smoking behavior.</td>
<td>57</td>
<td>December 2018</td>
</tr>
<tr>
<td>Oncken</td>
<td>NCT02048852</td>
<td>To examine the potential effect of reducing nicotine content or menthol or both in women of reproductive age.</td>
<td>320</td>
<td>December 2018</td>
</tr>
<tr>
<td>Rohsenow</td>
<td>NCT01989507</td>
<td>To determine the impact of very low nicotine content cigarettes in smokers with current or past year substance use disorders.</td>
<td>250</td>
<td>May 2018</td>
</tr>
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</table>
Take home point

More data always help, but we should be asking what we need

Potential benefits
- Reduced smoking
- Reduced dependence
- Increased quitting
- Reduced acquisition

Potential harms
- Compensatory smoking
- Discomfort/dysfunction
- Risk perception
- Smoker revolt
- Black market

Is it more likely than not that nicotine reduction will improve public health?
Putting nicotine reduction in context

Abstinence

Non-combusted products

Cigarettes

Least toxic

Continuum of Harm

Most toxic
Putting nicotine reduction in context

Abstinence

Non-combusted products

Cigarettes

Least toxic

Continuum of Harm

Most toxic
Putting nicotine reduction in context

Availability of alternatives may:
- Maximize public acceptability
- Reduce black market
- Reduce legal/trade concerns
- Reduce discomfort/dysfunction
- Facilitate smoking abstinence
Putting nicotine reduction in context

Nicotine reduction may minimize concerns
Dual use over abstinence
Gateway to smoking

Continuum of Harm

Abstinence

Non-combusted products

Cigarettes

Most toxic

Least toxic
Should New Zealand Reduce Nicotine in Combusted Tobacco?
The Case for Reducing Nicotine in New Zealand

• A clearly defined and supported goal of decreasing smoking prevalence to <5% by 2025
  • Current prevalence: 15% overall; 36% Māori
• Established “traditional” tobacco control measures (MPOWER)
• Reduced potential for an extensive black market
• Increasing interest in nicotine-containing e-cigarettes
• Advertising bans that enables control of messaging regarding the impact of reducing nicotine and the continued harms associated with burned tobacco
• Widespread acceptability of such a policy by smokers and non-smokers.
One potential approach

• Set a target date for the mandated nicotine reduction for all burned tobacco products.

• Allow immediate sale of
  • Reduced nicotine content cigarettes
    • Upper limit: 0.4 mg of nicotine content per g of tobacco
  • Nicotine-containing e-cigarettes

• Consider two adjunct policies for interim period
  • Differential taxation for combustible tobacco based on a threshold of nicotine content
    • 2-tier system based on upper limit of 0.4 mg nicotine per g of tobacco
    • Created primarily by large tax increases on high nicotine content cigarettes.
  • Package-level messaging that VLNC cigarettes are not less harmful, but may be less addictive

• Implement public service announcements to explain change in tobacco products, and the long-term plan to phase out tobacco products that are both highly addictive and highly toxic.

• Identify early-adopter communities who are motivated to implement a mandated nicotine reduction policy, and monitor the impact of this implementation.
Is the time right for the public health community to advocate for reducing nicotine in all combusted tobacco?
Thank you