Nicotine Reduction and Smoking
The potential impact and necessity of nicotine product standards for cigarettes?

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Funding
Research reported in this publication was supported by the National Institute on Drug Abuse and Food and Drug Administration Center for Tobacco Products (U54 DA031659). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.
Disclosures

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• **Lots of collaborators**: Dorothy Hatsukami, Neal Benowitz, Joe McClernon, Andrew Strasser, Jen Tidey, Suzanne Colby, Rachel Denlinger-Apte, Tracy Smith, Cassidy White, Joe Koopmeiners, Sharon Murphy, Steve Hecht, and all other faculty and staff associated with CENIC past and present.
The Tobacco Endgame
Eradicating a Worsening Epidemic

MPOWER provides a roadmap for the Tobacco Endgame

- Monitoring tobacco use and prevention policies
- Protecting people from tobacco smoke
- Offering help to quit tobacco use
- Warning about the dangers of tobacco
- Enforcing bans on tobacco advertising, promotion and sponsorship
- Raising taxes on tobacco for effective tobacco control
14% of Americans currently smoke cigarettes.
Whether to push or pull? Nicotine reduction and non-combusted alternatives - Two strategies for reducing smoking and improving public health

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Rationale for reducing nicotine

• Nicotine, through its neuropharmacological actions, motivates behavior. Currently, the primary target behavior is smoking.
• Cigarettes, as a means of nicotine delivery, are deadly
• Reducing nicotine in cigarettes will likely render them less reinforcing/addictive.
• If true, reducing nicotine could ...
  • Reduce initiation in naïve individuals
  • Increase cessation in current smokers
  • Reduce relapse in ex-smokers
• By changing behavior, nicotine reduction can improve health
Reducing nicotine decreases the number of cigarettes smoked.
Reducing nicotine decreases nicotine exposure.
Reducing nicotine *does not* lead to compensatory changes in how people smoke.

Smith et al., CEBP 2020
Reducing nicotine does not lead to compensatory changes in how people smoke.

“What my thoughts were and what the reality was was two totally different ideas. You know my thought was they’re going to be nasty. You’re not going to even taste anything. I’m going to smoke like a freight train to try to make up for the nicotine my body is craving and it ended up that it didn’t even come out that way.”

Participant from open label hotel study
Denlinger-Apte et al. DAD. 2021
Reducing nicotine is likely to *increase* cessation.

In the largest trial of non-treatment seekers to date, immediate reduction to 0.4 mg/g increased odds of abstinence at Week 20 (OR: 3.22)

*Hatsukami et al 2018*
Reducing nicotine is likely to increase cessation

“And so I’ve been able to cut down on smoking. I don’t seem to be as needy on the cigarettes.”

“It makes me want to just go ahead and quit. Put them down.”

“I actually finally feel like the cigarettes aren’t controlling me.”

Participant from open label hotel study
Denlinger-Apte et al. DAD. 2021
However, reducing nicotine leads to non-adherence
However, reducing nicotine leads to non-adherence and dropout.
Implications of non-adherence/non-completion
What role do alternatives sources of nicotine play?

• **Nicotine replacement**
  • **Design: 2x2**
    • Cigarette nicotine content
      • Very Low ("VLNC," 0.4 mg/g)
      • Normal ("NNC," 15.8 mg/g)
    • Transdermal nicotine
      • 14-21 mg patch (dose reductions PRN)
      • No patch
What role do alternatives sources of nicotine play?

- Nicotine replacement
  - VLNC cigarettes reduced smoking

Smith et al., 2019

![Graph showing smoking reduction over weeks with different nicotine treatments](image-url)
What role do alternatives sources of nicotine play?

- Nicotine replacement
  - VLNC cigarettes reduced smoking
  - Patch reduced smoking of NNC cigarettes, but added little to the effect of VLNCs
    - Other studies have found small effect of patch on VLNC use (Donny et al., 2009; Hatsukami et al., 2013)

-Smith et al., 2019
What role do alternatives sources of nicotine play?

Smith et al., 2019
All behavior is choice
-Herrnstein, 1970
What role do alternatives sources of nicotine play?

- Very low nicotine product standard
- Reduced appeal and addictiveness
- Behavior change
  - Quit altogether (with or without medication)
  - Completely switch to non-combusted alternatives
  - Dual use cigarettes (illicit or VLNC) and alternatives
  - Persistent use VLNC cigarettes
  - Switch to combusted alternatives
  - Switch to illicit cigarettes
What role do alternatives sources of nicotine play?

Nicotine reduction was associated with an increase in days using alternative products (most commonly e-cigarettes) AND Use of alternative products was associated with increased number of days abstinent from cigarettes

What role do alternatives sources of nicotine play?

- Focus of current trials: Nicotine reduction in the context of alternative sources of nicotine
Is nicotine reduction necessary? Are less harmful alternatives sufficient?
Alternatives may not be enough

*Figure 2. E-cigarette use among current adult cigarette smokers, Great Britain (2010 - 2019)*


*ASH, September 2019*
Alternatives may not be enough
Alternatives may not be enough

- Smoking
- Vaping

Derived from the Office of National Statistics, September 2021
Alternatives may not be enough

Figure 5. Main reason for not trying an e-cigarette among smokers (2019)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not want to substitute one addiction for another</td>
<td>16%</td>
</tr>
<tr>
<td>I am not addicted to smoking and don't need help to quit</td>
<td>12%</td>
</tr>
<tr>
<td>I do not know enough about them</td>
<td>11%</td>
</tr>
<tr>
<td>I do not want to quit smoking</td>
<td>9%</td>
</tr>
<tr>
<td>I do not think they would help me to quit or cut down</td>
<td>9%</td>
</tr>
<tr>
<td>I am concerned they are not safe enough</td>
<td>9%</td>
</tr>
<tr>
<td>Haven't got around to it yet</td>
<td>8%</td>
</tr>
<tr>
<td>They cost too much</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
<tr>
<td>I would be embarrassed to use them in public</td>
<td>4%</td>
</tr>
<tr>
<td>I do not like the way they look</td>
<td>4%</td>
</tr>
<tr>
<td>There are too many products to choose from</td>
<td>3%</td>
</tr>
<tr>
<td>I'm using other things to help me quit smoking</td>
<td>1%</td>
</tr>
<tr>
<td>They are too difficult to get hold of</td>
<td>0%</td>
</tr>
</tbody>
</table>

Unweighted base: GB current smokers who have not tried e-cigarettes; 2019, n=614

ASH, September 2019
Alternatives may not be enough

- They didn't feel like smoking a cigarette: 25%
- They didn't help me deal with cravings for smoking: 20%
- I only ever tried them to see what they were like: 16%
- Other: 11%
- Don't know/ can't remember: 6%
- I felt I was using them too often compared with smoking: 4%
- They kept leaking: 4%
- I was concerned they were not safe enough: 4%
- They cost too much: 4%
- They were difficult to use or refill: 3%
- I was embarrassed to use them in public: 1%
- They felt too much like smoking a cigarette: 1%
- Refills and replacements were not easily available: 1%
- A health professional advised me to stop: 1%

ASH, September 2019
Whether to push or pull? Nicotine reduction and non-combusted alternatives - Two strategies for reducing smoking and improving public health
What alternatives are necessary/sufficient in the context of reduced nicotine cigarettes?

• Flavors
• Nicotine delivery
A terminated trial – preliminary data

• Design: 2x2x2
  • Cigarette nicotine content
    • Very Low (“VLNC,” 0.04 mg/g)
    • Normal (“NNC,” 15.8 mg/g)
  • Vaping Device (e-liquid) nicotine content
    • Low (0.3%)
    • Moderate (1.8%)
  • Vaping Device (e-liquid) flavor options
    • Tobacco - (3) Tobacco/Menthol options
    • Range - (12) Tobacco/Menthol, Mint, Fruit, Dessert options

• Participants
  • History of smoking 5-50 cigarettes daily for past month
  • History of using vaping device on 2+ separate occasions, but less than 15 days in past month

White et al, in prep
# A terminated trial – preliminary data

## Study Timeline

<table>
<thead>
<tr>
<th>Date Range</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall 2017 - Summer 2018</td>
<td>Protocol development, IRB approval.</td>
</tr>
<tr>
<td>Fall 2018</td>
<td>Piloting.</td>
</tr>
<tr>
<td>Winter 2018/19</td>
<td>Enrolled and randomized first participants.</td>
</tr>
<tr>
<td>Fall 2019</td>
<td>~50 participants randomized.</td>
</tr>
<tr>
<td></td>
<td>Decided to end this trial early to shift efforts to an adaptable-design marketplace trial.</td>
</tr>
</tbody>
</table>

## Changes in Marketplace

- Rise in popularity of Juul reported
- PMTA submission deadline moved up to **May 2020**.
- Disposable products (i.e. PuffBar) becoming increasingly popular.

*White et al, in prep*
A terminated trial – preliminary data

White et al, in prep

Adjusted for baseline CPD, site, menthol status, and age group.
A terminated trial – preliminary data

White et al, in prep
A crowdsourcing study – Discrete Choice

Imagine one of the products below will be the only nicotine and tobacco product you have access to for the next week. Which product would you choose?

(1 of 18)

Option 1

**PRODUCT**

Cigarettes

**FLAVOR**

Your choice of non-menthol or menthol.

**NICOTINE CONTENT**

Low: About half as much nicotine as your usual cigarettes, per puff.

Select

Option 2

**PRODUCT**

Vaping Device

**FLAVOR**

Your choice of tobacco and menthol flavors.

**NICOTINE CONTENT**

Low: About half as much nicotine as your usual cigarettes, per puff.

Select

White et al, in prep
# A crowdsourcing study – Discrete Choice

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Cigarettes</th>
<th>Vaping Device</th>
</tr>
</thead>
</table>
| **Nicotine Content** | • **Very Low:** 95% less nicotine than your usual cigarettes, per puff.  
• **Low:** About half as much nicotine as your usual cigarettes, per puff.  
• **Normal:** The same amount of nicotine as your usual cigarettes, per puff. | • **Very Low:** 95% less nicotine than your usual cigarettes, per puff.  
• **Low:** About half as much nicotine as your usual cigarettes, per puff.  
• **Moderate:** The same amount of nicotine as your usual cigarettes, per puff. |
| **Flavor**     | • Your choice of menthol or non-menthol               | • Your choice of **tobacco and menthol flavors**  
• Your choice of **tobacco, menthol, fruit and dessert flavors** |
A crowdsourcing study – Discrete Choice

White et al, in prep
Summary
The Science Behind Nicotine Reduction

• Nicotine levels at or below 2.4 mg/g reduce smoking and exposure to harmful constituents
• Smokers switched to very low nicotine content cigarettes do NOT compensate; moderate reductions may lead to compensation
• Immediate reduction is likely to lead to more rapid declines in smoking and improved public health, but will also present greater challenges in terms of discomfort and adherence.
• Use of very low nicotine cigarettes is likely to increase smoking cessation by reducing dependence, craving, and withdrawal and by increasing quit attempts and the probability of achieving abstinence.
• Reducing nicotine in cigarettes leads to significant non-adherence (i.e., participants use non-study cigarettes)
Summary
The Implementation of Nicotine Reduction

• Smokers are likely to demonstrate a wide range of behavioral changes following implementation of a low nicotine product standard ranging from abstinence to persistent smoking to use of alternative sources of nicotine.

• In the absence of policies (like nicotine reduction) that reduce the abuse liability of cigarettes, many smokers will fail to try and/or persist in using alternative nicotine delivery systems.

• If the goal is to maximize improvements in public health, both nicotine reduction and harm reduction approaches are likely to be necessary but neither may be sufficient to *rapidly* end the devastation caused by smoking.
Thank you for listening

Drugs disrupt the circuits that give us free will. It is really the essence of addiction.

- Nora Volkow, 168th Annual Meeting of the American Psychiatric Association