Nicotine Reduction and Smoking in Vulnerable Populations

Jennifer W. Tidey, Ph.D.
Professor of Behavioral & Social Sciences
Associate Dean for Research
Brown University School of Public Health
Support & Disclosures

- This research that I will be discussing today was funded by grants from NIDA and the FDA Center for Tobacco Products. I do not have any funding from tobacco or e-cigarette companies.
- The content is solely my responsibility and does not necessarily represent the official views of the NIH or the FDA.
Why Study Nicotine Reduction in Vulnerable Populations?

- The 2009 Tobacco Control Act authorized the FDA to set product standards for cigarettes, including nicotine content. The FDA must consider the risks and benefits to the population as a whole.
- Vulnerable populations are those at elevated risk for tobacco-related health harms due to high rates of smoking and low rates of cessation.
- A reduced-nicotine standard could reduce dependence and increase the likelihood of quitting among those vulnerable to persistent tobacco use.
- However, vulnerable populations could also experience unintended negative consequences of a reduced-nicotine standard.
  - Increases in negative affect and other psychiatric symptoms
  - Increases in smoking in efforts to overcome these effects
  - Increases in alternative substance use
Populations of Special Relevance to the FDA Center on Tobacco Products

<table>
<thead>
<tr>
<th>Youth</th>
<th>Socioeconomically disadvantaged populations</th>
<th>Racial/ethnic minorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underserved rural populations</td>
<td>People with MHCs</td>
<td>People with SUDs</td>
</tr>
<tr>
<td>Military/veteran populations</td>
<td>Pregnant women or women of reproductive age</td>
<td>Sexual and gender minorities</td>
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Very Low Nicotine Content Cigarettes

<table>
<thead>
<tr>
<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>Research Cigarettes</td>
<td>variable</td>
<td>variable</td>
</tr>
<tr>
<td>Normal Nicotine</td>
<td>15.8</td>
<td>~0.73</td>
</tr>
<tr>
<td>Reduced Nicotine</td>
<td>5.2</td>
<td>~0.24</td>
</tr>
<tr>
<td>Very Low Nicotine</td>
<td>2.4</td>
<td>~0.11</td>
</tr>
<tr>
<td>Very Low Nicotine</td>
<td>1.3</td>
<td>~0.06</td>
</tr>
<tr>
<td>Very Low Nicotine</td>
<td>0.4</td>
<td>~0.03</td>
</tr>
<tr>
<td>Very Low Nicotine</td>
<td></td>
<td>~9 or 13</td>
</tr>
</tbody>
</table>
1. Acute exposure
   - VLNC cigarettes reduce abstinence-induced craving, withdrawal and smoking in adults with and without schizophrenia (Tidey et al., 2013);
     no compensatory smoking topography (Tidey et al. 2016);
     cognitive effects of VLNCs reversed with NRT (AhnAllen et al. 2015)
   - VLNC cigarettes reduce cigarette reinforcement in 3 vulnerable populations including adults with affective disorders (Higgins et al., 2017).

2. 6-week exposure
   - Secondary analysis found that people with elevated baseline depression responded similarly to those with lower depression (Tidey et al., 2017).
   - In an RCT, VLNC cigarettes reduced cigarette use and smoke intake in adults with schizophrenia or bipolar disorder (Tidey et al., 2019).

3. 12-week exposure
   - In an RCT, VLNC cigarettes reduced smoking, breath CO and dependence in 3 vulnerable populations including adults with affective disorders (Higgins et al., 2020).
6-Week Use of VLNCs in Adults with Lower vs. Higher Depressive Symptoms

<table>
<thead>
<tr>
<th>Screen</th>
<th>Baseline</th>
<th>Weeks 1 - 6</th>
<th>AA</th>
<th>Follow Up</th>
</tr>
</thead>
</table>

Usual Brand

Weekly Laboratory Visits

Study cigarettes provided free of charge:
1. 15.8 mg nicotine/g tobacco
2. 2.4, 1.3 or 0.4 mg nicotine/g tobacco

Measures: Total cigarettes per day, nicotine & toxicant exposure, dependence, craving, withdrawal, mood, psychiatric symptoms, cognitive performance, topography, quit attempts, effects of 24-hr abstinence

Secondary analysis of Donny et al. 2015 NEJM
Tidey et al. 2017 Nicotine Tob Res
Effects on CPD and Nicotine Exposure

Lower BL depressive symptoms

Higher BL depressive symptoms

Tidey et al. 2017 *Nicotine Tob Res*
Craving & Withdrawal During Abstinence

Lower BL depressive symptoms

- UB, 15.8 mg/g
- 0.4 - 2.4 mg/g

Higher BL depressive symptoms

- UB, 15.8 mg/g
- 0.4 - 2.4 mg/g

Tidey et al. 2017 *Nicotine Tob Res*
Effects on Depression

Lower BL depressive symptoms

Higher BL depressive symptoms

Tidey et al. 2017 Nicotine Tob Res
6-Week Use in Adults with Schizophrenia or Bipolar Disorder

- Screen
- Baseline
- Weeks 1 - 6
- AA
- Follow Up

Usual Brand

Weekly Laboratory Visits

Study cigarettes provided free of charge:
1. 15.8 mg nicotine/g tobacco
2. 0.4 mg nicotine/g tobacco

Measures: Total cigarettes per day, nicotine & toxicant exposure, dependence, craving, withdrawal, mood, psychiatric symptoms, topography, quit attempts, effects of 24-hr abstinence

Tidey et al. 2019, *Nicotine Tob Res*
Effects on Smoking

**Total Cigarettes Per Day: Change from Baseline**

Number of Cigarettes

```
BL  Wk1  Wk2  Wk3  Wk4  Wk5  Wk6
```

**Breath Carbon Monoxide Level**

Mean (ppm)

```
BL  Wk1  Wk2  Wk3  Wk4  Wk5  Wk6
```

**Study Cigarettes Per Day: Change from Baseline**

Number of Cigarettes

```
BL  Wk1  Wk2  Wk3  Wk4  Wk5  Wk6
```

Tidey et al. 2019, *Nicotine Tob Res*
Product Appeal

Tidey et al. 2019, Nicotine Tob Res
## 12-Week Use in Adults from 3 Vulnerable Populations

<table>
<thead>
<tr>
<th>Screen</th>
<th>Baseline</th>
<th>Weeks 1 - 12</th>
<th>AA</th>
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### Weekly Laboratory Visits

Study cigarettes provided free of charge:
1. 15.8 mg/g nicotine content
2. 2.4 mg/g nicotine content
3. 0.4 mg/g nicotine content

### Measures:
Total cigarettes per day, nicotine & toxicant exposure, dependence, craving, withdrawal, mood, psychiatric symptoms, cognitive performance, topography, quit attempts, effects of 24-hr abstinence

### 3 Vulnerable Populations (n = 775):
1. Disadvantaged women of childbearing age (n = 258)
2. Adults receiving treatment for OUD (n = 260)
3. Adults with current or lifetime depression or anxiety disorders (n = 257)

Higgins et al., 2020; *JAMA Network Open*
Changes in Cigarette Consumption With Reduced Nicotine Content Cigarettes Among Smokers With Psychiatric Conditions or Socioeconomic Disadvantage: 3 Randomized Clinical Trials

Stephen T. Higgins, PhD; Jennifer W. Tidey, PhD; Stacey C. Sigmon, PhD; Sarah H. Heil, PhD; Diann E. Gaalema, PhD; Dustin Lee, PhD; John R. Hughes, MD; Andrea C. Villanti, PhD; Janice Y. Bunn, PhD; Danielle R. Davis, PhD; Cecilia L. Berger, PhD; Joanna M. Streck, BA; Maria A. Parker, PhD; Mollie E. Miller, PhD; Michael DeSarno, MS; Jeff S. Priest, PhD; Patricia Cioe, PhD; Douglas MacLeod, MS; Anthony Barrows, BA; Catherine Markesich, BA; Roxanne F. Harfmann, BA

A Total cigarettes

B Study cigarettes

Nicotine and tobacco content
- 15.8 mg/g
- 2.4 mg/g
- 0.4 mg/g

Higgins et al., 2020; JAMA Network Open
Effects on Dependence

Higgins et al., 2020; *JAMA Network Open*
Effects on Depression

*eFigure 6. Beck Depression Inventory Score by Dose*

Panel shows Beck Depression Inventory (BDI) Scores for each of the three nicotine-content-cigarette doses (0.4, 2.4, and 15.8 mg/g). Data points are collapsed across participants, populations, and 12-week study period; error bars represent ± SEM. Data points not sharing a superscript letter differed significantly by dose.

Higgins et al., 2020; *JAMA Network Open*
Adults Who Use Other Substances

1. Acute exposure
   - VLNC cigarettes reduce cigarette reinforcement in 3 vulnerable populations including adults with OUD (Higgins et al., 2017).

2. 6-week exposure
   - Secondary analysis found that current cannabis use did not moderate the effects of VLNCs on smoking, nicotine dependence, craving, or nicotine exposure; VLNCs did not increase cannabis use (Pacek et al. 2016).
   - Secondary analysis in alcohol users found no evidence of compensatory alcohol use or binge drinking (Dermody et al. 2016).

3. 12-week exposure
   - In an RCT, VLNC cigarettes reduced smoking, breath CO and dependence in 3 vulnerable populations including adults with OUD (Higgins et al., 2020).

4. 20-week exposure
   - Secondary analysis found that baseline drinking and SMAST score did not moderate the effects of VLNCs on Week 20 CPD or CO; smaller reduction in TNE among higher alcohol users; VLNCs reduced daily alcohol use and binge drinking (Dermody et al. 2021).
Adults in Treatment for OUD

Participants with OUD:
No difference on total CPD, dependence severity, CO
More non-study CPD early in the trial; more e-cig, NRT and smokeless tobacco use
Less sensitive to effects of VLNCs on nicotine intake, toxicant exposure, craving

Higgins et al., 2020; JAMA Network Open
Adults with Socioeconomic Disadvantage

1. Acute exposure
   - VLNC cigarettes reduce cigarette reinforcement in 3 vulnerable populations including low SES women of reproductive age (Higgins et al., 2017).

2. 12-week exposure
   - In an RCT, VLNC cigarettes reduced CPD, breath CO and dependence in 3 vulnerable populations including low SES women (Higgins et al., 2020).

3. 18-week gradual reduction
   - In an RCT, low SES adults in the RNC group had higher attrition and lower CPD, nicotine exposure and CO. Among completers, RNC group was more likely to make a quit attempt and more likely to be abstinent (9% vs 3%) one month later (Krebs et al. 2020).

4. 20-week exposure
   - Secondary analysis of a 20-week RCT found that regardless of race, gender or educational attainment, immediate reduction resulted in reductions in CPD, nicotine and toxicant exposure; Black participants had smaller reduction in TNE than White participants (Carroll et al., 2021).
Adults with Socioeconomic Disadvantage

Krebs et al. 2020; Nicotine & Tobacco Research
Adults with Socioeconomic Disadvantage

Krebs et al. 2020; *Nicotine & Tobacco Research*
Adults with Other Vulnerabilities

1. Effects of VLNCs on smoking, nicotine/toxicant exposure and abstinence were smaller in menthol smokers than non-menthol smokers (Denlinger et al., 2019).

2. A secondary analysis found that having 0-1, 2-3 or ≥4 cumulative vulnerabilities (rural residence, OUD, affective disorder, low educational attainment, poverty, unemployment, physical disability) was associated with CPD but did not moderate response to VLNCs (Higgins et al., 2021).

3. Acute exposure study in pregnant women found that VLNCs were less satisfying, rewarding and reinforcing than UB (Heil et al., 2020).
Menthol Smokers

**Cigarettes Per Day**

- **Mean CPD**
  - Baseline
  - Week 20

**Urinary Total Nicotine Equivalents**

- **Geometric Mean (nmol/mg)**
  - Baseline
  - Week 20

**CO-Verified Abstinence at Week 20**

- **% of Participants**
  - Randomized
  - Completers

**Urinary CEMA**

- **Geometric Mean (nmol/mg)**
  - Baseline
  - Week 20

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Denlinger-Apte et al. 2019; Nicotine & Tobacco Research
Youth and Young Adults

1. Acute exposure
   - VLNC cigarettes reduced abstinence-induced craving, withdrawal and negative affect in smokers aged 15-19 (Cassidy et al., 2018); VLNCs were less reinforcing (Cassidy et al., 2019); no moderation of CO boost by menthol (Denlinger-Apte et al. 2019)
   - Secondary analysis in 3 vulnerable populations found that 18-24 year-olds were more sensitive to the effects of nicotine dose on demand than older adults (Davis et al. 2019).

2. 3-week exposure
   - VLNC cigarettes reduced cigarettes per day in youth ages 15-19 (Cassidy et al. 2020).

3. 6-week gradual reduction
   - Secondary analysis found that 18-24 year-olds found VLNCs less satisfying and rewarding, and smoked fewer CPD, than older adults at Week 2; no differences at Week 6 (Cassidy et al. 2019).

4. 20-week exposure
   - Secondary analysis of a 20-week RCT found that age group (18-24 vs. 25+) did not moderate effects of immediate reduction on CPD reduction; positive subjective effects of cigarettes were lower among 18-24 year-olds (Cassidy et al. 2021).
Cassidy et al. 2019 Nicotine & Tobacco Research

Younger vs. Older Adults

Week 2
- Smoking Satisfaction
  - Usual Brand
  - 15.8 mg/g
  - 5.2 mg/g
  - 2.4 mg/g

Week 6
- Smoking Satisfaction
- Psychological Reward

Cassidy et al. 2019 Nicotine & Tobacco Research
Younger vs. Older Adults

Cassidy et al. 2019 *Nicotine & Tobacco Research*
Younger vs. Older Adults

Cassidy et al. 2021 *Nicotine & Tobacco Research*
Populations of Special Relevance to the FDA Center on Tobacco Products

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To date, effects of VLNCs in vulnerable populations are very similar to effects in less vulnerable populations.

- Reduction in smoking without increasing psychiatric symptoms, substance use or compensatory smoking

- Extent of CPD reduction is ~ 4-7 CPD
  - Studies enroll non-treatment-seeking participants and provide free cigarettes
  - Some indication of increased treatment seeking and quitting

- Supplementary nicotine may help with adherence and enhance reductions in smoking
  - Study of 16-week use of VLNC cigarettes with and without e-cigarettes in 3 vulnerable adult populations is currently underway; lab study of VLNC cigs with and without e-cigs in youth/young adults is underway
Collaborators

- CENIC team: Eric Donny, Dorothy Hatsukami, Suzanne Colby, Tonya Lane, Rachel Cassidy, Rachel Denlinger-Apte, Patricia Cioe, Joe McClernon, Neal Benowitz, Andrew Strasser, the CENIC Biostats Core and Biomarkers Core, our outstanding staff and trainees, and the rest of the CENIC team.

- UVM TCORS team: Steve Higgins, Diann Gaalema, Stacey Sigmon, Sarah Heil, Andrea Villanti, John Hughes, Jan Bunn, Dustin Lee, our outstanding staff and trainees, and the rest of the UVM TCORS team.