Tobacco Regulation Across the Continuum of Harm

Tracy T. Smith, Ph.D.
Cigarettes are deadly and most smokers want to quit

Babb et al., 2017 *MMWR*
Continuum of Harm

- Combustible cigarettes
- Other Combustible Products
- E-cigarettes
- NRT
- Abstinence

Bulk of the harm, Most opportunity for impact
Why do people smoke?

- **nicotine**
- **smoking**
- **Primary reinforcement**
Set product standards for the improvement of public health considering both:

- Current smokers
- Naive individuals

Product standards including nicotine (but cannot require reduction to zero)

Family Smoking Prevention and Tobacco Control Act

FDA NEWS RELEASE

FDA Announces Plans for Proposed Rule to Reduce Addictiveness of Cigarettes and Other Combusted Tobacco Products

Potential Rule Would Propose to Establish a Maximum Level of Nicotine in Cigarettes with the Goal of Reducing Youth Use, Addiction and Death

For Immediate Release: June 21, 2022
How would a mandated reduction in nicotine content impact smoking behavior?
Human Clinical Trial Design

Assigned to either receive:

- 15.8 mg nicotine / g tobacco
- 0.4 mg nicotine / g tobacco
  >97% reduced

Smith et al., 2019 AJPM
Impact of nicotine reduction on smoking behavior in clinical trials

N=120
Smith et al., 2019 AJPM
Impact of nicotine reduction on smoking behavior in clinical trials

N=120
Smith et al., 2019 AJPM
Will smokers compensate for a reduction in nicotine content?
Clinical trials do not show sustained increase in CPD

N=120
Smith et al., 2019 AJPM
Many smokers are noncompliant

Nardone et al., 2016
Would smokers compensate if they were unable to access normal nicotine content cigarettes?
### Hotel Inpatient Study

<table>
<thead>
<tr>
<th>Normal Nicotine Content Cigarettes</th>
<th>Very Low Nicotine Content Cigarettes</th>
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<tbody>
<tr>
<td>Day 1</td>
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<td>Day 2</td>
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<td>Day 5</td>
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Cohort of Participants

Washout week

Cohort of Participants

N=16
Cigarettes for Purchase
Cigarettes for Purchase

• Any money left in participants’ accounts was provided to them at the end of the week
Cigarettes per day

Smith et al., 2020 CEBP
Cigarettes per day

Smith et al., 2020 CEBP
Expired Carbon Monoxide

- **Expired Carbon Monoxide (ppm)**
- **Check In**
  - NNC
  - VLNC

**Smith et al., 2020 CEBP**
What about changes in smoking intensity within each cigarette?

White et al., 2022 Nicotine and Tobacco Research
Expectancies

“My initial reaction was I’m gonna have to smoke probably two to one or three to one just to get the same amount.” –47 yo, M

“What my thoughts were and what the reality was is 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 didn’t even come out that way.” –38 yo, F

“I was just thinking I would have to keep lighting up cigarettes back-to-back just to get-like five cigarettes, I was thinking, just to feel like I smoked one. But then, and after trying them, it wasn’t like that at all.” –33yo, M

“Oh sh*t” –51 yo, F

Denlinger-Apte et al., 2021 Drug and Alcohol Dependence
Withdrawal?

“I’ve been like—I’m not freaking out, I’m not upset, I’m not depressed, I feel fine. I feel kinda tired though, you know, kinda drained.” – 51 yo, F

“I would say I feel about the same as I always do….if anything, I’ve been more—maybe more hungry.” – 33 yo, M

”Slightly more irritated about it.” –50 yo, M

Denlinger-Apte et al., 2021 Drug and Alcohol Dependence
Dependence

“when I go home now I’m thinking. “Do I just not even smoke when I get back in that car with my husband?” you know. Should I do that you know, or do I actually pick up another cigarette, you know… Cause I think I can actually quit now.” –51 yo, F

“I find I’m able to play cards without dying for a cigarette, to go and read a book without having that cigarette in my hand. I’m not having the urge to literally keep that cigarette pack next to me.”—36 yo, F

“I smoked more on Monday, I still smoked a decent amount on Tuesday, but once Wednesday got here it’s like my cravings for wanting to smoke and my really need to smoke has really come down a whole lot. It’s like the desire of I need a cigarette is not as strong.” –38 yo, F

*Denlinger-Apte et al., 2021 Drug and Alcohol Dependence*
A mandated reduction in nicotine content is likely to...

- Reduce cigarettes smoked per day among smokers unmotivated to quit
- Unlikely to produce sustained compensation
- Reduce initiation of cigarette smoking among individuals who are naïve to nicotine
- Increase cessation among smokers motivated to quit
- Similar effects observed a variety of vulnerable subpopulations
There are other interventions aimed at reducing appeal and addictiveness....more on this later.

FDA NEWS RELEASE

FDA Commits to Evidence-Based Actions Aimed at Saving Lives and Preventing Future Generations of Smokers

Efforts to ban menthol cigarettes, ban flavored cigars build on previous flavor ban and mark significant steps to reduce addiction and youth experimentation, improve quitting, and address health disparities

For Immediate Release: April 29, 2021
Combustible cigarettes

Other Combustible Products

Most Harmful

Least Harmful

E-cigarettes

NRT Abstinence

Continuum of Harm
How should we regulate non-combustible products?
Prevalence of E-cigarette Use Among Adults

Cornelius et al., 2020 MMWR
What is the impact of e-cigarette use on cigarette smoking for adults?
Pilot trial investigating impact of e-cigarettes on smoking

Daily smokers
N=31

3-weeks smoking as usual
• Low Wattage
• High Nicotine Concentration
• No Customization
• Simple to Use

3-weeks sampling
• Variable Wattage
• Variable Nicotine Concentration
• Highly Customizable
• Complicated to Use

3-weeks sampling

MUSC Health
Changing What’s Possible | MUSChealth.org
E-cigarette Use

Change in CPD
% Trying to Quit Smoking

Change in CO
E-cigarettes can reduce cigarette smoking, even among smokers not instructed to switch.
Can e-cigarettes help smokers abstain from smoking better than FDA-approved medications?
Smokers who have already tried to quit and failed with FDA-approved medications N=30

Daily diaries reporting tobacco use and tobacco/medication use throughout.

N=20

1 week: Set a Target Quit or Switch Date
Use medication or e-cigarette ad libitum while continuing to smoke

Target Switch Date

Final Visit

N=10

4-weeks: Instructions to Switch or Quit completely

Target Quit Date

Final Visit

Current N=13

N=13
Smokers who have already tried to quit and failed with FDA-approved medications N=225

N=150

OR

1 week pre-switch

Target Switch Date

8 weeks, switch completely

Follow up to 6-mo, encouraged to get more as desired

Outcomes: Self-reported tobacco and medication use, expired carbon monoxide, urinary NNAL, respiratory function (self-reported and spirometry)

N=75

OR

1 week pre-quit

Target Quit Date

8 weeks, quit completely

Follow up to 6-mo, encouraged to get more as desired
What are determinants of “successful” switching to e-cigarettes?
Nicotine delivery and sensorimotor cues are likely important
Impact of Nicotine Concentration and Device Wattage
Impact of Nicotine Concentration and Device Wattage

Ongoing, N=74
E-cigarettes....

• Among adults, are most used in current and former smokers
• Have the potential to reduce cigarette smoking and dependence in adult smokers, even without explicit instructions to switch
  • Future research should investigate intentional switching
• Device characteristics likely important, nicotine is critical determinant in all tobacco products
  • What level of nicotine is required? How does this compare to the level adolescents find appealing?
• Are popular among non-smoking youth
  • Many youth want to quit vaping and future studies should develop and test interventions
FUTURE
Continuum of Harm

Most Harmful

Combustible cigarettes

Other Combustible Products

E-cigarettes

NRT

Abstinence

Least Harmful
Menthol: A broader definition of harm

Delveno et al., 2020
Menthol: A broader definition of harm

A. Menthol may increase smoking initiation
   i. Youth and new smokers are more likely to smoke menthol cigarettes

B. Menthol may increase cigarette dependence and hinder quitting
   i. Menthol smokers are more likely to try to quit and less likely to be successful

C. Menthol contributes to tobacco use disparities. Menthol is more used among vulnerable groups including African Americans, women, members of the LGBT community, individuals with low income and low education, and those with comorbid mental illness
   i. African Americans make up 30% of menthol smokers, but 80% of African American smokers use menthol cigarettes
FDA NEWS RELEASE

FDA Commits to Evidence-Based Actions Aimed at Saving Lives and Preventing Future Generations of Smokers

Efforts to ban menthol cigarettes, ban flavored cigars build on previous flavor ban and mark significant steps to reduce addiction and youth experimentation, improve quitting, and address health disparities

For Immediate Release: April 29, 2021
Figure 1. Conceptual framework illustrating the impact of a cigarette and e-cigarette menthol ban on tobacco use outcomes for menthol smokers. Once treatment effects have been estimated in a clinical trial sample, it is critical to model their impact in the population. These policies are likely to also impact nonsmokers, including e-cigarette users, but those pathways are not the focus of this trial and not displayed in Figure 1.
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How would a menthol ban for cigarettes and/or e-cigarettes impact smoking behavior, switching to e-cigarettes, and quitting?
Current Menthol Smokers (N=240)

Cigarette Assignment

Menthol

Non menthol
Trial Design

Cigarette Assignment

- Menthol
- Non menthol

E-cigarette Flavor Assignment
- Menthol
- Tobacco
Trial Design

Cigarette Assignment
- Menthol
- Non menthol

E-cigarette Flavor Assignment
- Menthol
- Tobacco

Status Quo
- No Ban
- n=60
Trial Design

Cigarette Assignment

Menthol

Non menthol

E-cigarette Flavor

Menthol

Tobacco

Status Quo
No Ban
n=60

Cigarette only menthol ban condition
n=60
Trial Design

Cigarette Assignment

- Menthol
  - Status Quo
    - No Ban
      - n=60
  - Cigarette and e-cigarette menthol ban
    - n=60
- Non menthol
  - Cigarette only menthol ban condition
    - n=60
Trial Design

- **E-cigarette Flavor Assignment**
  - Menthol
    - E-cigarette only menthol ban condition
      - n=60
  - Non menthol
    - Cigarette and e-cigarette menthol ban
      - n=60

- **Tobacco**
  - Status Quo
    - No Ban
      - n=60
  - Cigarette only menthol ban condition
    - n=60

MUSC Health
Medical University of South Carolina
Changing What’s Possible | MUSChealth.org
Baseline

Usual Brand Provided
Study product provided free of charge

... everyone also has the option to take home NRT each week.
... everyone also has the option to take home NRT each week.

**Outcomes:** Cigarettes per day, e-cigarette use (including switching), ability to remain abstinent in Week 7, NRT use, quit attempts, subjective effects, cigarette and e-cigarette dependence

Aim 3 will describe the heterogeneity, calibrate the effect to the US adult menthol population, and model the impact on death and life years lost.
Combustible cigarettes

Other Combustible Products

Most Harmful

E-cigarettes

NRT Abstinence

Least Harmful

Continuum of Harm
How should we regulate non-combustible products?
What about flavors?
Submit Tobacco Product Applications for Deemed Tobacco Products

Resources for Applicants Required to Submit by September 9, 2020

Applications for many e-cigarettes and other new deemed tobacco products that were on the market as of Aug. 8, 2016 were required to be submitted to FDA by Sept. 9, 2020. The deadline has now passed. If you have submitted an application and are looking for information on next steps, visit the "What Happens After I Submit the Application?" section on this page. If you are looking for information on FDA compliance and enforcement, visit the "Why Must I Comply?" section on this page.

On Sept. 9, 2021, CTP Director Mitch Zeller provided an update on FDA's progress on tobacco product application review and related enforcement.
FDA NEWS RELEASE

FDA Denies Marketing Applications for About 55,000 Flavored E-Cigarette Products for Failing to Provide Evidence They Appropriately Protect Public Health

Action Marks First Marketing Denial Order. Orders Must be Removed from the Market.

FDA NEWS RELEASE

FDA Permits Marketing of E-Cigarette Products, Marking First Authorization of Its Kind by the Agency

FDA STATEMENT

FDA Makes Significant Progress in Science-Based Public Health Application Review, Taking Action on Over 90% of More Than 6.5 Million ‘Deemed’ New Tobacco Products Submitted
We’ve made **significant progress** in the months since, working diligently to better understand these products and, as of today, taking action on about 93% of the total timely-submitted applications. This includes issuing Marketing Denial Orders (MDO) for more than 946,000 flavored ENDS products because their applications lacked sufficient evidence that they have a benefit to adult smokers sufficient to overcome the public health threat posed by the well-documented, alarming levels of youth use of such products.
Do non-tobacco flavors in e-cigarettes better promote switching than tobacco flavors?
Preliminary data—CONNECT STUDY

Current Cigarette Smokers (N=638, nationwide)

E-cig n=427

Flavor choices with each shipment: classic tobacco, menthol, apple melon, blue and blackberry, iced fruit

Control n=211

2 weeks

2 weeks

Follow up until 6-mo

Dr. Matt Carpenter
Reason to believe they may be important for switching

Data are preliminary
Reason to believe they may be important for switching

Data are preliminary
Did flavor matter?

**Figure 2**

Data are preliminary
Current Cigarette Smokers (N=1500, nationwide)

2 weeks pre-switch

开关日

12 weeks, switch completely

12 weeks follow up

Outcomes: Cigarettes per day, e-cigarette use (including switching), expired carbon monoxide
Summary

• FDA has the authority to regulate tobacco products to improve public health, and these regulations need to consider both users and non-users.

• Regulations that reduce the appeal and addictiveness of combusted tobacco are likely to have the biggest impact.
  • Nicotine reduction, if it can get done, is likely the most effective possible intervention.
  • Menthol is also likely to impact outcomes for current menthol users. Upcoming RCT on menthol.

• Regulations that reduce the appeal of non-combusted products, like e-cigarette flavoring regulations, are complicated because they impact both users and non-users.
  • Upcoming RCT on flavors, Upcoming intervention trial for smokers who can’t quit.
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Thank You and Questions