E-cigarettes and the Debate about Tobacco Harm Reduction

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Conflict of Interest Statement

• I am a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications.

• I am not promoting or discussing these companies or their products in this presentation.
A 27 year old woman with moderate persistent asthma presents to establish care. Her symptoms are well controlled on inhaled fluticasone and salmeterol.

She smokes and asks if she should use electronic cigarettes to help her quit smoking. She has tried smoking cessation medications before but was unable to stop smoking.
Smoking prevalence has decreased in U.S. but with marked social disparities

- 2017: 14% adult smoking prevalence
- 40 million smokers
- 30% adults below poverty line
- High prevalence in those with mental illness and substance abuse
- Smoking is major cause of premature death in alcoholics and people with schizophrenia

World-wide smoking is still one of the most important causes of premature mortality and morbidity
Getting smokers to quit as soon as possible is essential for public health
Projected Global Mortality from Smoking 2000-2050

Cumulative Deaths (millions)

Year

Current Course
Prevention Effect
Prevention and Treatment Effect
Treatment Effect

Henningfield and Slade, FDLI, 1998
Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to "Nicotinic Cholinergic Receptors"
NICOTINE ADDICTION CYCLE

CIGARETTE SMOKING → NICOTINE ABSORPTION → AROUSAL MOOD MODULATION PLEASURE

CRAVING FOR NICOTINE TO SELF-MEDICATE WITHDRAWAL SYMPTOMS → DRUG ABSTINENCE PRODUCES WITHDRAWAL SYMPTOMS → TOLERANCE AND PHYSICAL DEPENDENCE
Nicotine

Addictive Combusted Tobacco Use

7 Million Deaths Annually
Nicotine Replacement Medications: not very satisfying; low adoption
C'est une E-cigarette
Nicotine Addiction and Tobacco Harm Reduction
Definition of Harm Reduction

Harm reduction refers to policies, programs and practices that aim to reduce the harms associated with the use of psychoactive drugs in people unable or unwilling to stop. The defining feature is the focus on prevention of harm, rather than the prevention of drug use itself...

Harm Reduction International
Nicotine

Addictive Tobacco Use

¼ Billion Deaths

Clean Nicotine Delivery Systems

Harm Reduction
Nicotine in cigarettes and smokeless tobacco is a drug and these products are nicotine delivery devices under the Federal Food, Drug, and Cosmetic Act.

_U.S. Food and Drug Administration_  
Aug. 11, 1995
Despite extraordinary progress in tobacco control and prevention, tobacco use remains the leading cause of preventable disease and death in the United States. Combustible cigarettes cause the overwhelming majority of tobacco-related disease and are responsible for more than 480,000 U.S. deaths each year. Indeed, when used as intended, combustible cigarettes kill half of all long-term users.¹ With the tools provided to the Food and Drug Administration (FDA) under the Family Smoking Prevention and Tobacco Control Act of 2009, the agency has taken consequential steps to prevent sales of tobacco products to children, expand the science base for understanding traditional and newer tobacco products, and conduct public education campaigns. But the agency needs to do more to protect Americans;
FDA Regulatory Framework with a Focus on Nicotine

- Smoking causes 480,000 deaths per year
- The core problem is not nicotine itself, but the delivery mechanism (combustible tobacco)
- Goal to reduce the addictiveness of cigarettes
- Focus on nicotine and support innovation to promote harm reduction
- Consider the continuum of risk of nicotine-containing products
Continuum of Risk

Addictiveness/Appeal vs. Toxicity
International Debate on the Role of E-cigarettes in Tobacco Control Policy

• EC use has the potential to reduce harm and eventually end cigarette use by allowing smokers to switch to a safer product.

  vs

• EC use has the potential to increase cigarette use by promoting adolescent nicotine addiction, providing a gateway to smoking for non-smokers, and via dual use reducing quitting. ECs are less harmful than cigarettes, but not harmless.
E-cigarettes: an evidence update
A report commissioned by Public Health England

“The current best estimate is that e-cigarette use is around 95% less harmful to health than smoking”

August, 2015
FDA News Release

FDA takes new steps to address epidemic of youth e-cigarette use, including a historic action against more than 1,300 retailers and 5 major manufacturers for their roles perpetuating youth access

Warning letters and civil money penalty complaints to retailers are largest coordinated enforcement effort in agency history; FDA requests manufacturers provide plan for mitigating youth sales within 60 days; warns it may restrict flavored e-cigarettes to address youth epidemic
Alternative Nicotine Delivery Devices: Electronic Cigarettes and Heat-not-burn Devices
Battery

Absorbent material: cotton or silica holds nicotine dissolved in propylene glycol or vegetable glycerin

Atomizer/coil: heats and aerosolizes nicotine

Nicotine aerosol

Cartridge, mini, or cigalike

2nd generation (eGo-type)

3rd generation (mods)
Heated Tobacco Products
(Will not be covered in this talk)

Global State of Tobacco Harm Reduction Report, 2018
Epidemiology of E-cigarette Use

• U.S. general population ever use: 0.6% 2009; 12.6% 2014; 15.4% 2016

• Among U.S. smokers: 2.6% daily use; 5.6% some days; 13.1% experimenting; 38.8% previously used, but not now.

• 0.1 – 3.8% never smokers have tried EC
Most common reasons for E-cigarette use in adults

• Less harmful than cigarette smoking
• Trying to reduce or quit smoking
• Use in smoke-free areas
• Financial burden of cigarette smoking
• Lifestyle appeal
Main components of EC aerosol

- Nicotine
- Propylene glycol (PG)
- Vegetable glycerine (VG)
- Flavorants
- Particles
- Various thermal degradation products
E-cigarette Voltage and Aldehyde Emissions

(Sleiman et al. Envir Sci Tech 2016)
55 Gallon Drum of 100mg Nicotine

Price: $11,000.00
SKU: NIC 10055
Brand: Liquid Nicotine by Vapor World
Current Stock: Out of stock
* Select your Base: PG, VG

The selected product combination is currently unavailable.
Nicotine

• Nicotine levels in Ecigs vary from 0 to 70 mg/ml.
• Nicotine delivery depends on temperature of coil, nicotine content of liquid and PG/VG ratio
• pH of liquid may influence sensory characteristics, site of nicotine absorption and absorption rate
• Higher nicotine concentration results in high pH. Nicotine salts result in lower pH.
Nicotine PK with E-cigarette use during standardized session

Plasma nicotine (ng/mL) vs. Time after last of 15 puffs (min)

- Subj 2, cartridge
- Subj 6, tank
- Subj 7, tank

(St. Helen, Addiction 2015)
Circadian Plasma Nicotine and Cotinine Concentrations with ad lib smoking and vaping (N=36), UCSF
E-Liquid nicotine concentrations do not predict daily nicotine exposure

<table>
<thead>
<tr>
<th>Nicotine Concentration</th>
<th>Blood/saliva Cotinine</th>
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<tbody>
<tr>
<td>4.1 mg/ml</td>
<td>430 ng/ml *</td>
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<tr>
<td>22.5 mg/ml</td>
<td>316 ng/ml *</td>
</tr>
<tr>
<td>59 mg/ml</td>
<td>237 ng/ml (r 145 – 313)</td>
</tr>
</tbody>
</table>

* Data from Wagener et al., Tob Control 2016
Do E-cigarettes Promote Quitting Smoking?

- Past clinical trials of poor quality and using early generation devices suggest similar efficacy to nicotine patch. First quality study published 2019.
- UK cross-sectional and cohort studies – estimate 16,000 to 28,000 additional long term quitters per year associated with EC use
- Some U.S. longitudinal studies find substantial odds ratios for EC use and quitting
- Some U.S. cross-sectional and cohort studies suggest that EC use might deter smokers from quitting
A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.
Pragmatic trial, UK NHS

- 866 participants
- ECig Starter kit vs. Choice of NRT
- Behavioral Support for 4 weeks
- 80% ECig use in Quitters at 1 year

CO-verified smoking abstinence at one year

E-Cigarettes: 18.0%
NRT: 9.9%

Hajek et al, NEJM, 2019
Health Concerns with E-cigarette Use
Adverse Health effects of E-cigarettes

- Health effects of long-term use are unknown.
- Based on toxicant analyses and a few clinical studies, EC use is likely to be much less harmful than cigarette smoking.
- Concerns about long-term pulmonary and cardiovascular effects of carbonyls, nicotine, flavorings, and particulate exposure.
- Passive vapor exposure is likely to be much less, if at all, harmful to nonsmokers, although nonsmokers are exposed to nicotine.
Major Safety Concerns for Nicotine

- Addiction
- Cardiovascular Disease
- Reproductive Toxicity
- Infectious disease risk
- Cancer

- Definite
- Probable
- Probable
- Possible
- Unlikely
National Academy of Sciences
Engineering and Medicine Report

- Published 2018
- Comprehensive lit review
- Short and long term health effects
  - E-cigarette users
  - Vulnerable populations
  - Nonusers exposed to secondhand aerosol
The Ascendancy of JUUL
E-Cig 4-wk Share Performance Overall

4-wk retail share performance

Source: Nielsen Total US xAOC/Convenience Database & Wells Fargo

Campaign for Tobacco Free Kids, JUUL and Youth
Juul Pod Mod.
START WITH YOUR JUULPOD

Remove colored cap & insert cartridge end into device. Voila - it becomes your mouthpiece as well as the flavorful engine that powers JUUL.

No buttons or switches, just draw to get it going - carefully at first, it may seem strong to first-timers.

CONSULT THE INDICATOR

The indicator glows during use to reflect pull strength and while charging. When pod is inserted, gently tap device twice to show charge level:

- Green = high
- Yellow = medium
- Red = low

CHARGE IT

Stand device in magnetic USB charger. Reaches full charge in 1 hour.
Nicotine PK Comparing JUUL and Pall Mall

10-Puff Sessions

Ad Libitum Sessions

Baseline-Adjusted Nicotine Plasma Concentration (ng/ml)

Error Bars ± 2SE

Wynne et al, SRNT Poster, 2018
Nicotine Chemical Forms
Free Base and Protonated (Salt)

\[ pK_a = 8.01 \]

Pankow et al, Chem Res Tox, 2018
Free Base Nicotine Fraction in Commercial E-liquids

Flavor (nicotine) | \( \alpha_{fb} \)
--- | ---
‘Placid’ (3 mg/mL) | 0.03
JUUL ‘Fruit Medley’ (58 mg/mL) | 0.05
JUUL ‘Crème Brulee’ (56 mg/mL) | 0.07
‘Maui’ (6 mg/mL) | 0.28
‘Taurus’ (3 mg/mL) | 0.46
‘No. 88’ (5 mg/mL) | 0.68
‘Galactica’ (3 mg/mL) | 0.70
‘Snake Oil’ (12 mg/mL) | 0.72
‘Snow White’s Demise’ (12 mg/mL) | 0.79
‘Maui’ (27 mg/mL) | 0.80
‘Zen’ (17 mg/mL) | 0.84

Pankow et al, Chem Res Tox, 2018
Clinical Pharmacology of JUUL

Summary

• High concentration of nicotine as benzoate salt
• Easy to inhale high nicotine aerosol due to low pH
• Temperature control reduces generation of thermal degradation products
• Small inhaled volumes along with temperature control reduces toxicant exposure
• Reports of daily use and use for pharmacologic effects suggests high abuse and high therapeutic potential
Are E-cigarettes Harming Youth?
National Youth Tobacco Survey

Past 30-Day Product Use by High School Students (9th - 12th Grade)

- Cigarettes
- E-Cigarettes

Prevalence (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cigarettes</th>
<th>E-Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>2012</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>2013</td>
<td>12%</td>
<td>3%</td>
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<td>2014</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>2015</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>2016</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>2017</td>
<td>11%</td>
<td>12%</td>
</tr>
</tbody>
</table>
National Youth Tobacco Survey

Past 30-Day Use by 6th - 12th Grade E-Cig Users

Prevalence (%)

- 1-2 Days
- 3-5 Days
- 6-9 Days
- 10-19 Days
- 20-29 Days
- All 30 Days
Number of teens who vape has jumped 75% this year, new study finds

Published: Sept 20, 2018 7:54 p.m. ET

About 20% of high school students used e-cigarettes in past 30 days, federal data shows

That would equate to about 3 million, or about 20% of high-school students, up from 1.73 million, or 11.7% of high-school students in the most recently published federal numbers from 2017.
“Nobody smokes cigarettes. You go to the bathroom, there’s a zero percent chance that anyone’s smoking a cigarette and there’s a 50-50 chance that there’s five guys Juuling”

- Connecticut High School Senior
christinazayas • Follow
New York, New York

christinazayas When smoking cigarettes is not an option, I've turned to @juulvapor. Read why, via the link in my bio! #JUULmoment #ad 🤡

Load more comments
soheatherblog Love this look!!
illraven Love the look
priscillathecreator I love his shot of you
cosmicchristine Love this look and going to try this out

1,515 likes
NOVEMBER 13, 2017

Introducing JUUL - Smoking Evolved
JUULvapor

https://youtu.be/OEj3tkca5HQ
Published on May 31, 2016
Regular e-cig use remains low among young people

1.7% of 11-18 year olds reported at least weekly use in Great Britain in 2018

Vaping continues to be associated with smoking. Regular use of e-cigs remains very low among never smokers (0.2% of 11-18 year olds in 2018)
Nicotine and Adolescent Brain Development

Nicotine interferes with prefrontal cortex maturation
Adolescent Behavior and the Brain

• Increased risk-taking, impulsivity, novelty-seeking
• Increased vulnerability to initiation and subsequent addiction to drugs
• Incomplete development of the prefrontal cortex: impaired decision making, impulse control and executive function
The JUUL Dilemma: potential benefits

• High nicotine content means good nicotine delivery with relatively low intake of aerosol
• Less aerosol exposure and temperature control results in less toxicant exposure
• Easy to use and relatively inconspicuous
• Possibly the most effective and safest e-cigarette to aid smoking cessation in adults
The JUUL Dilemma: potential harm

- Epidemic use among adolescents and college students
- Easy for non-smokers to inhale high doses of nicotine
- Easy to conceal
- Will this lead to primary nicotine addiction, and if so, what are the long term health consequences?
Other Ongoing E-cigarette Debates

• Tobacco industry vs independent manufacturers and vape shops – is regulatory policy supporting the tobacco industry?
• Tobacco harm reduction vs eliminating nicotine use – does our society accept nicotine addiction with some associated harm as a trade-off for no more cigarette smoking?
• Availability of e-liquid flavors: attractive to adults vs not attractive to kids
• Promoting vs refusing the use of ECs for smoking cessation – UK and France: training vape shop owners to be smoking cessation counselors; providing ECs to pregnant smokers who cannot quit.
Establishing a Nicotine Threshold for Addiction

- **Goal:**
  - To prevent nicotine addiction in youth.

- **Threshold for Addiction:**
  - Dose to establish and maintain addiction
    ~ 5 mg/day.

- **Proposal:**
  - A gradual reduction of nicotine content of cigarettes over 10-15 years.

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Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy

![Graph showing the reduction of cigarette and clean nicotine availability over years with an addiction threshold.](graph.png)
The extent of nicotine reduction across cigarette brands and other forms of combustible tobacco (roll your own, little cigars, pipe tobacco) must be uniform.
6-week Nicotine Content Taper: 75% reduction in nicotine intake, with sustained reduction on usual brand

Benowitz et al, CEBP 2007; 16:2479
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
21 CFR Part 1130
[Docket No. FDA–2017–N–6189]
RIN 0910–AH86

Tobacco Product Standard for Nicotine Level of Combusted Cigarettes

AGENCY: Food and Drug Administration, HHS.
ACTION: Advance notice of proposed rulemaking.
Potential Public Health Effects of Reducing Nicotine Levels in Cigarettes in the United States

Benjamin J. Apelberg, Ph.D., M.H.S., Shari P. Feirman, Ph.D., Esther Salazar, Ph.D., Catherine G. Corey, M.S.P.H., Bridget K. Ambrose, Ph.D., M.P.H., Antonio Paredes, M.S., Elise Richman, M.P.H., Stephen J. Verzi, Ph.D., Eric D. Vugrin, Ph.D., Nancy S. Brodsky, Ph.D., and Brian L. Rostron, Ph.D., M.P.H.
Apelberg Simulation of Effects of Mandatory Nicotine Reduction

- U.S. Population-based simulation model, 2016 to 2100
- Prediction: by year 2100 more than 33 million youth and young adults who would have become regular smokers would not start
- Prediction: 5 million smokers would quit within 1 year of implementation, and 13 million with 5 years
The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts

Tammy O. Tengs, Sc.D.,* Sajjad Ahmad, Ph.D., Jennifer M. Savage, B.A., Rebecca Moore, B.A., and Eric Gage, M.A.

Health Priorities Research Group, University of California, Irvine, CA, USA

Available online 8 July 2004
Tengs Simulation of Population Health Impact of Mandatory Nicotine Reduction

Smoking prevalence likely to decline to 5%, with resultant gain of 137 million QALYs over 50 years.

“Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population.”

Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game

Neal L. Benowitz, Eric C. Donny, Dorothy K. Hatsukami
Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy

![Graph showing the relationship between time and nicotine availability.](image)
Regulatory Implications

• Reducing the nicotine content of cigarettes is considered by many as the fastest route to eliminating smoking and its devastating health effects

• Regulatory decisions should consider a potential complementary role of ENDS and cigarette nicotine content reduction

• ENDS should have adequate nicotine, deliver nicotine sufficiently quickly to be reinforcing, and have acceptable sensory characteristics (including flavor) to be consumer-acceptable to support switching from cigarettes
What should the practitioner do regarding E-cigarettes and smoking cessation?
My position

If a patient has failed initial treatment, has been intolerant to or refuses to use conventional smoking cessation medication, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt.

*AHA Policy Statement on Electronic Cigarettes, Circulation 2014*
Counseling your Patient

• The EC is likely to be much less toxic than cigarette smoking, but no long term safety studies

• The products are unregulated

• ECs contain variable (and unpredictable) levels of toxic chemicals. Avoid use of high voltage, high temperature devices

• Consider setting a quit date for EC use (unless needed to prevent relapse to smoking)

• Do NOT continue cigarette smoking
What to Tell Youth about E-cigarettes

• E-cigarettes are not harmless
• E-cigarette use can result in nicotine addiction, which may have adverse effect on brain development
• E-cigarette use can cause respiratory symptoms such as cough or worsening asthma, and might increase the risk and severity of respiratory infections
FDA Regulatory Challenge

To facilitate the development of non-combusted nicotine delivery devices that are:

• Attractive substitutes for cigarettes for adult smokers
• Do not promote nicotine addiction in youth
• Have minimal generation of toxic constituents
Tobacco Control is Flying into New Territory