

# E-cigarettes and the Debate about Tobacco Harm Reduction

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**University of California**  
**San Francisco**

**ASCPT Annual Meeting**  
**March 15, 2019**



# 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.

# Clinical Vignette

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.

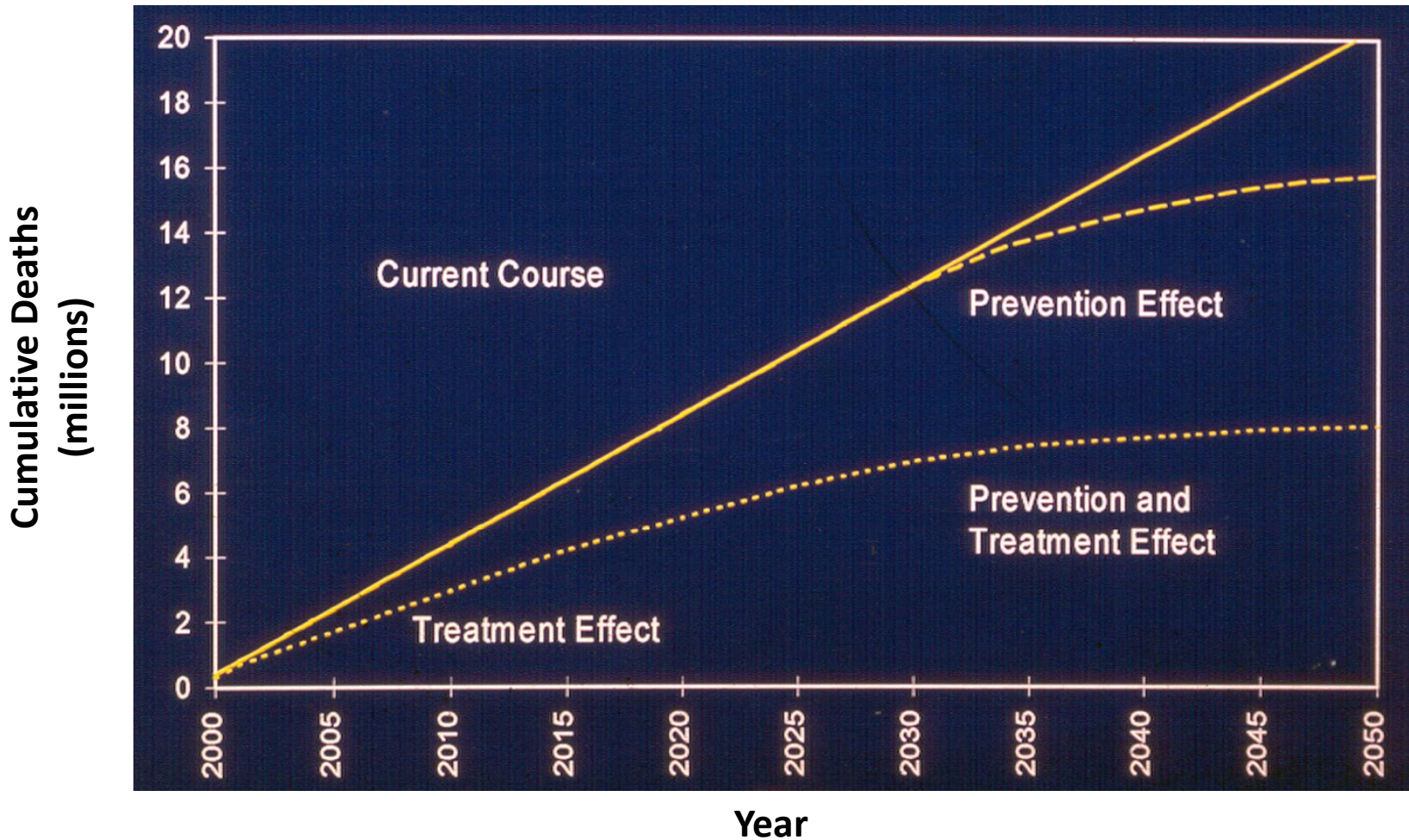
# **Smoking prevalence has decreased in U.S. but with marked social disparities**

- 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

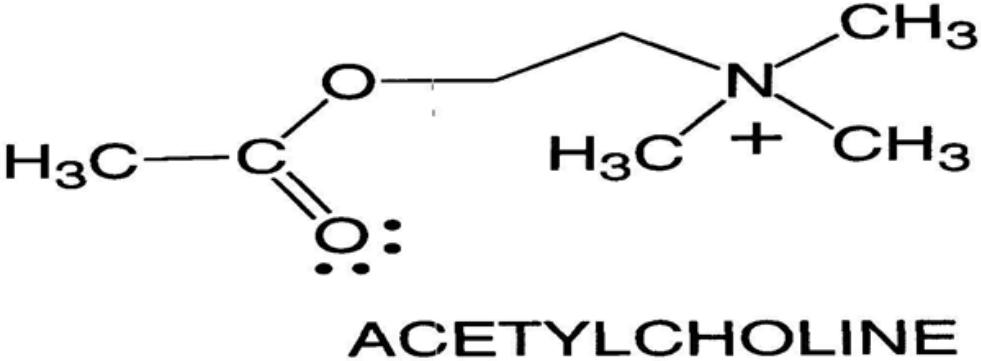
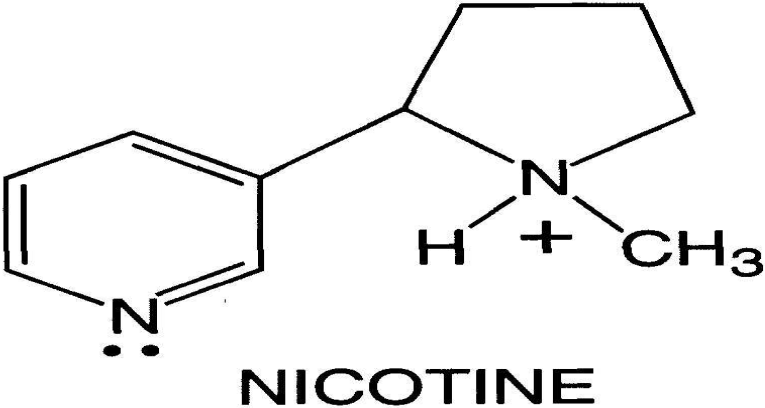
**World-wide smoking is still one of the most important causes of premature mortality and morbidity**

**Getting smokers to quit as soon as possible is essential for public health**

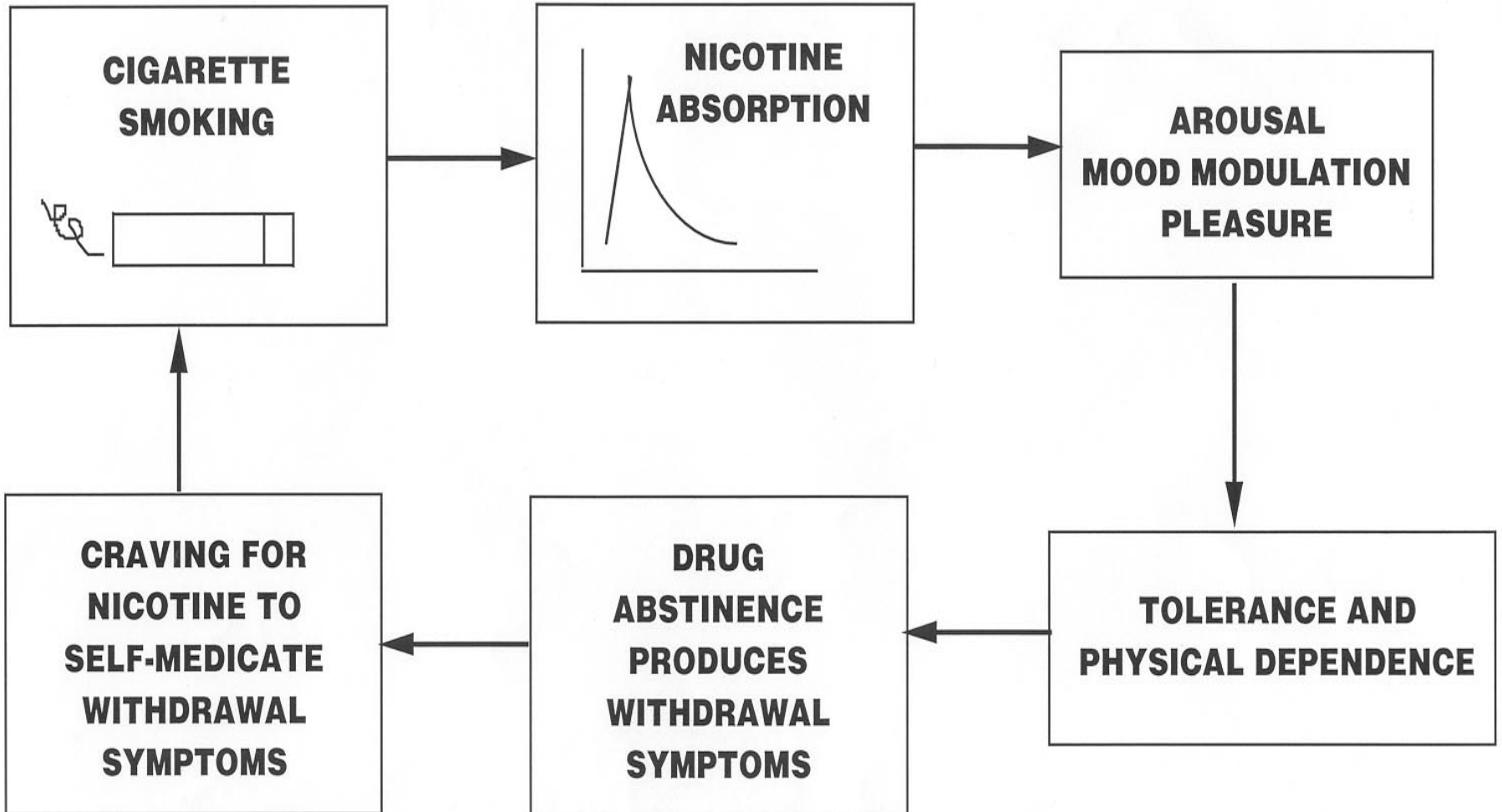
# Projected Global Mortality from Smoking 2000-2050



# Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to “Nicotinic Cholinergic Receptors”



# NICOTINE ADDICTION CYCLE





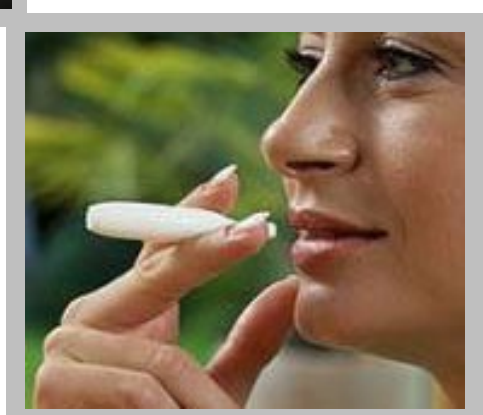
**Nicotine**

```
graph TD; A[Nicotine] --> B[Addictive Combusted Tobacco Use]; B --> C[7 Million Deaths Annually];
```

**Addictive Combusted Tobacco Use**

**7 Million Deaths Annually**

# Nicotine Replacement Medications: not very satisfying; low adoption



## Hon Lik - 2000



# 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**

```
graph TD; Nicotine --> AddictiveTobaccoUse[Addictive Tobacco Use]; AddictiveTobaccoUse --> CleanNicotineDeliverySystems[Clean Nicotine Delivery Systems]; AddictiveTobaccoUse --> Deaths[1/4 Billion Deaths]; CleanNicotineDeliverySystems --> HarmReduction[Harm Reduction];
```

**Addictive Tobacco  
Use**

**Clean Nicotine  
Delivery Systems**

**1/4 Billion Deaths**

**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*

Fed. Reg. Vol. 60, No. 155

Aug. 11, 1995



# Family Smoking Prevention and Tobacco Control Act (P.L.111-31) 2009



The NEW ENGLAND JOURNAL of MEDICINE

PERSPECTIVE

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# A Nicotine-Focused Framework for Public Health

Scott Gottlieb, M.D., and Mitchell Zeller, J.D.

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.<sup>1</sup> 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;

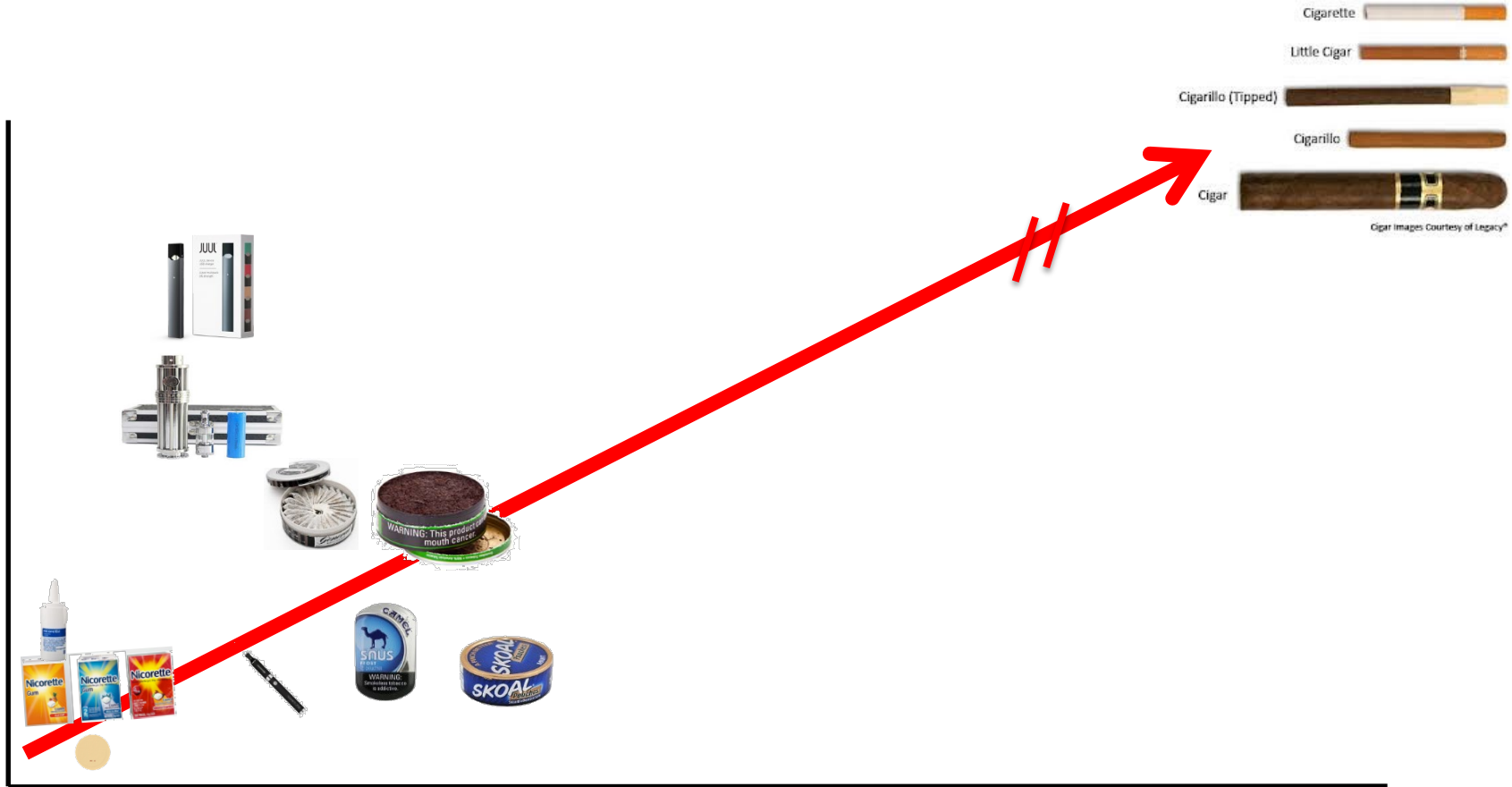
*Gottlieb and Zeller, NEJM, 2016*

# **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



Toxicity

- Cigarette
  - Little Cigar
  - Cigarillo (Tipped)
  - Cigarillo
  - Cigar
- Cigar Images Courtesy of Legacy®

# 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.



Public Health  
England

Protecting and improving the nation's health

# **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*

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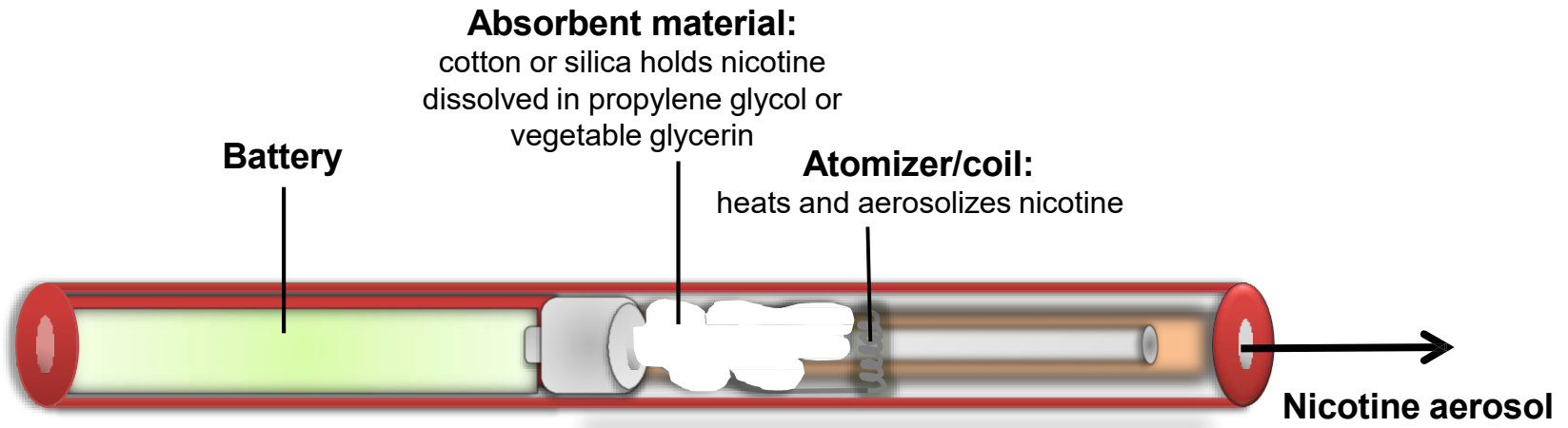
**For Immediate Release**

September 12, 2018

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# **Alternative Nicotine Delivery Devices: Electronic Cigarettes and Heat-not-burn Devices**





**Cartridge, mini,  
or cigalike**



**2<sup>nd</sup> generation  
(eGo-type)**



**3<sup>rd</sup> generation  
(mods)**



# Heated Tobacco Products

(Will not be covered in this talk)



# 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

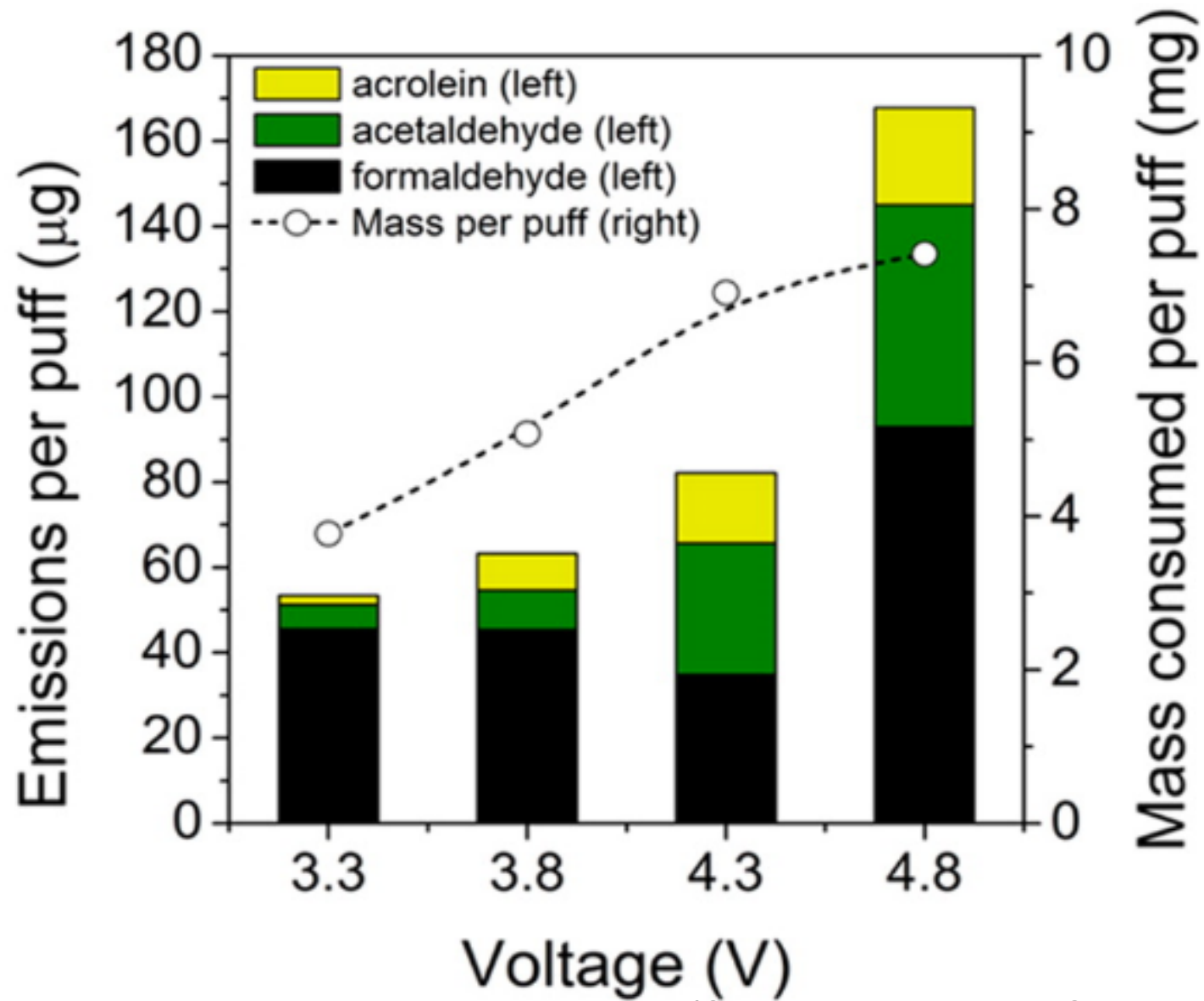
# Most common reasons for E-cigarette use in adults

- 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)

Home > Bulk > Liquid Nicotine > 55 Gallon Drum of 100mg Nicotine

## 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:

The selected product combination is currently unavailable.

### Add to Wish List

Click the button below to add the 55 Gallon Drum of 100mg Nicotine to your wish list.

### You May Also Like...

Wholesale Liquid  
100mg



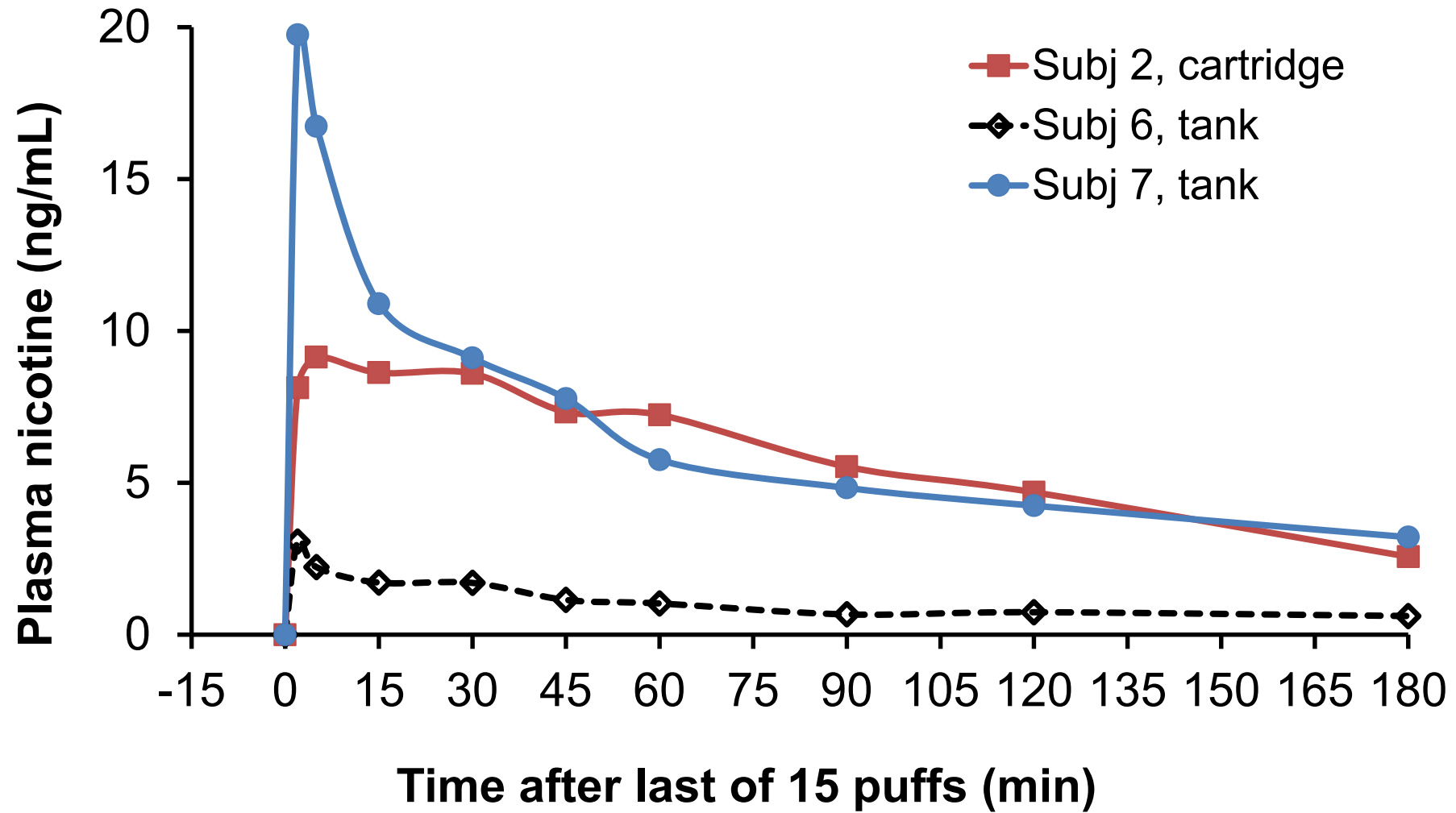
Share this product:

# Nicotine

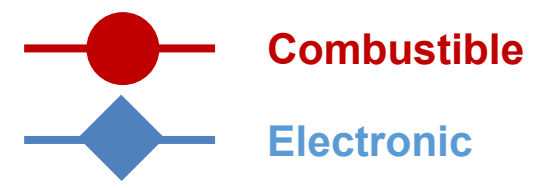
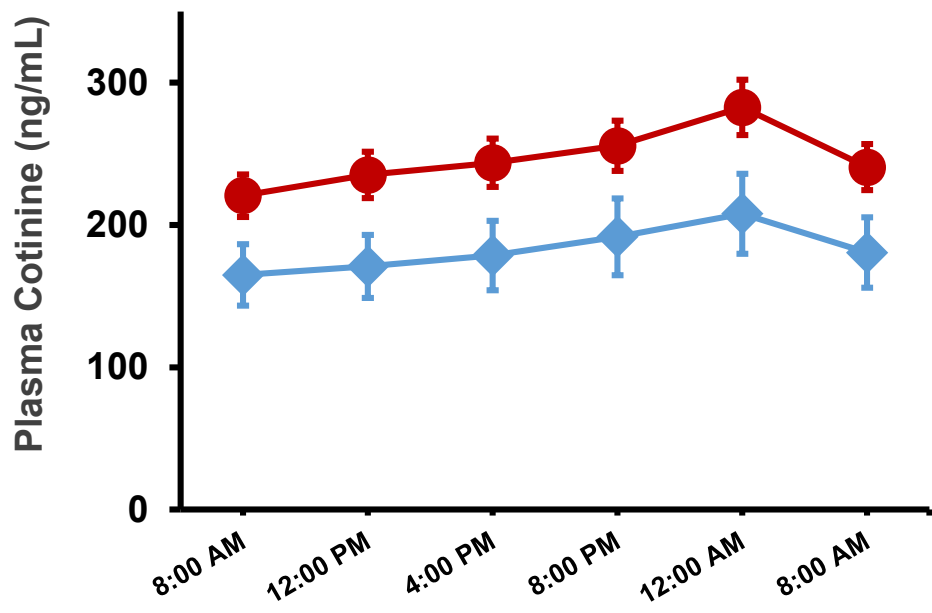
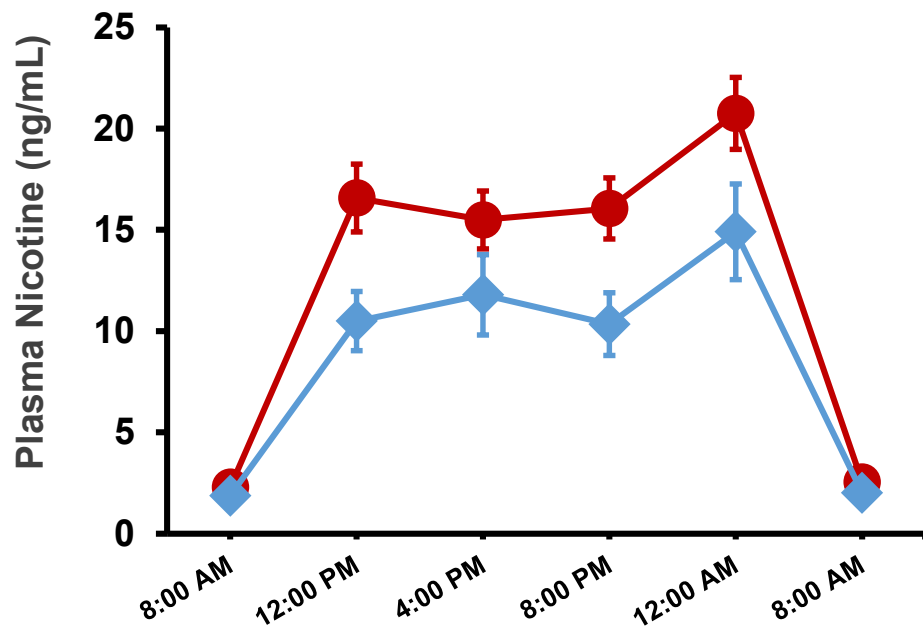
- Nicotine levels in Ecigs vary from 0 to 70 mg/ml.
- Nicotine delivery depends on temperature of coil, nicotine content of liquid and PG/VG ratio
- pH of liquid may influence sensory characteristics, site of nicotine absorption and absorption rate
- Higher nicotine concentration results in high pH.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



# Nicotine PK with E-cigarette use during standardized session



# 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



**Nicotine Concentration**

4.1 mg/ml

**Blood/saliva  
Cotinine**

430 ng/ml \*



22.5 mg/ml

316 ng/ml \*



59 mg/ml

237 ng/ml  
(r 145 – 313)



\* 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

ORIGINAL ARTICLE

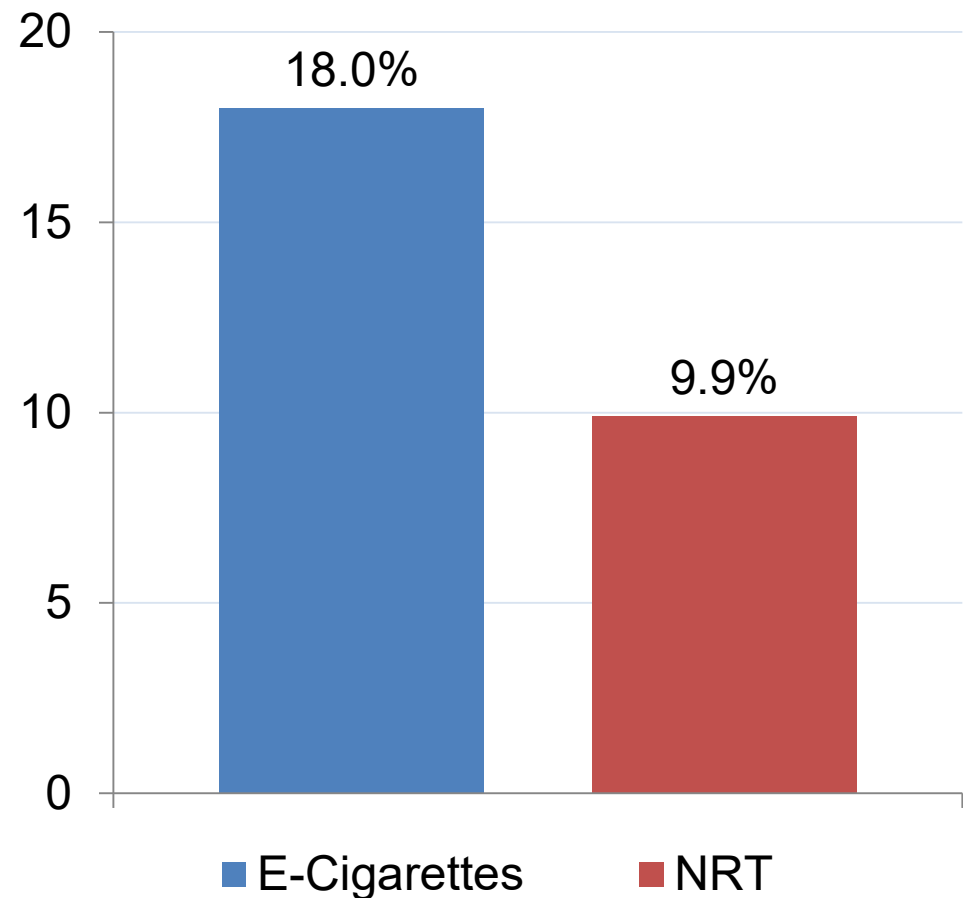
# A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

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



# Health Concerns with E- cigarette Use

# Adverse Health effects of E-cigarettes

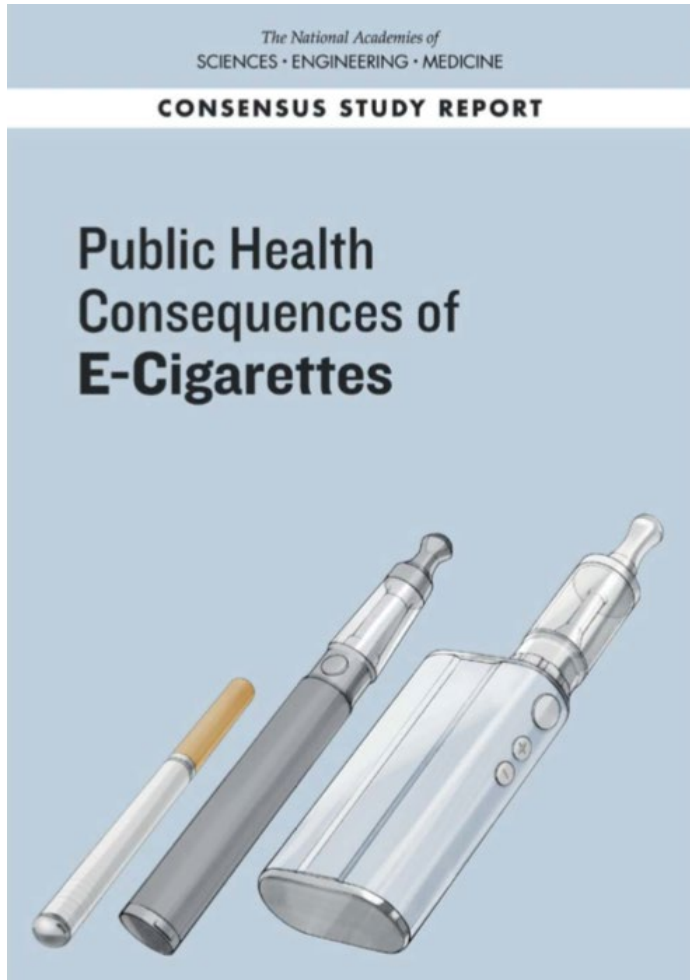
- Health effects of long-term use are unknown
- Based on toxicant analyses and a few clinical studies, EC use like to be much less harmful than cigarette smoking
- Concerns about long term pulmonary and cardiovascular effects of carbonyls, nicotine, flavorings and particulate exposure
- Passive vapor exposure 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





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.



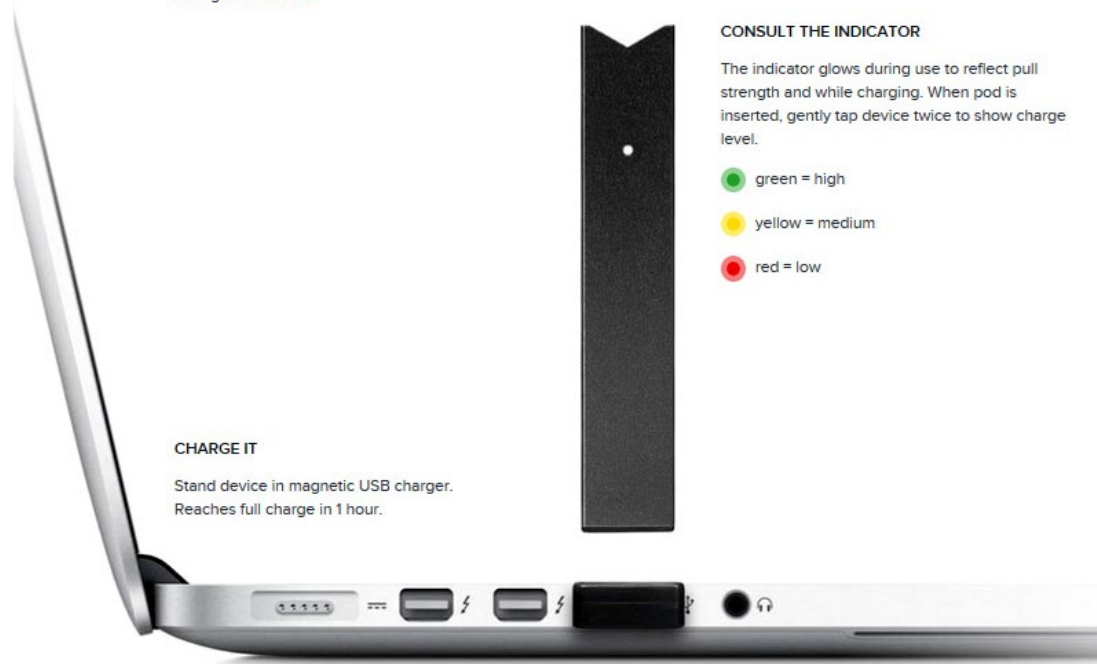
#### CONSULT THE INDICATOR

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

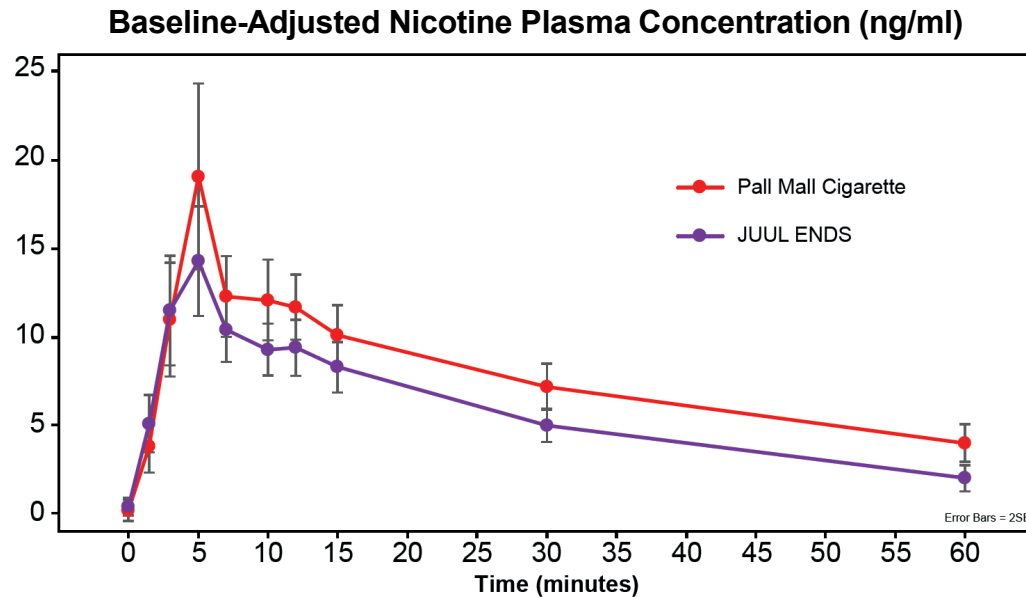
#### CHARGE IT

Stand device in magnetic USB charger.  
Reaches full charge in 1 hour.

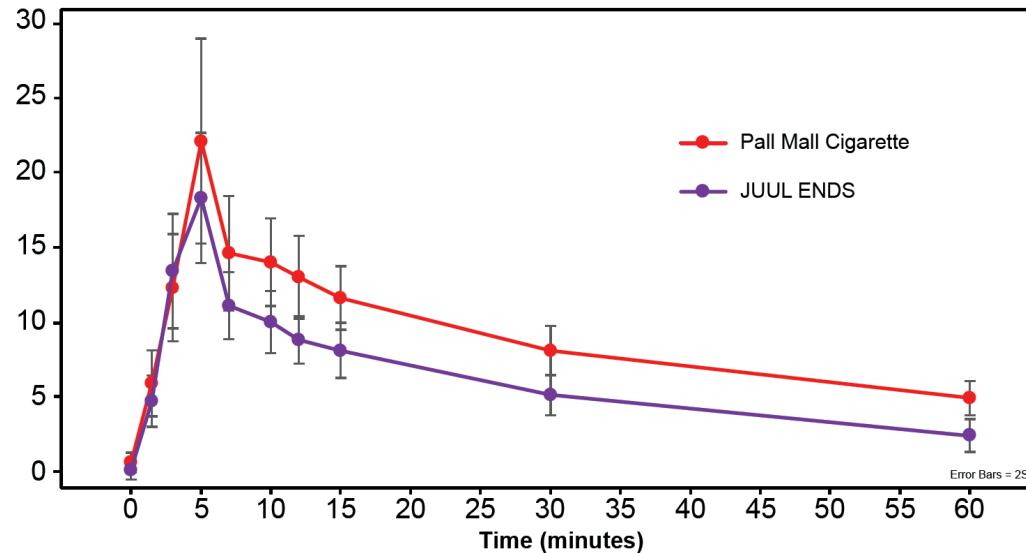


# Nicotine PK Comparing JUUL and Pall Mall

## 10-Puff Sessions



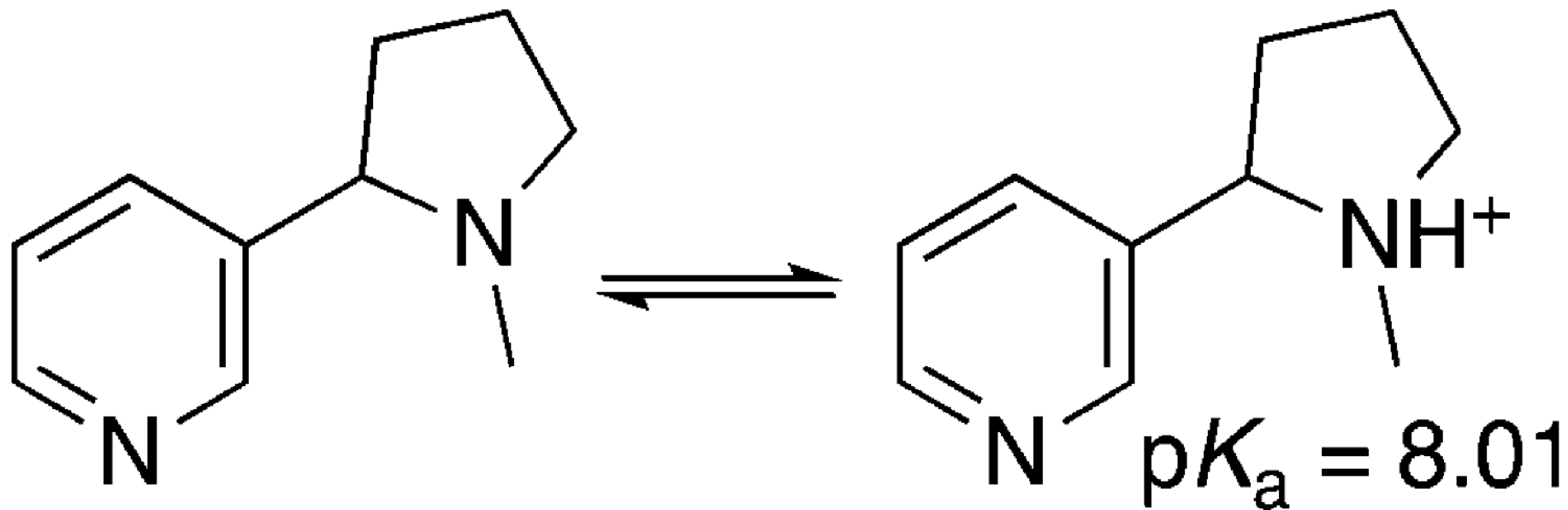
## Ad Libitum Sessions



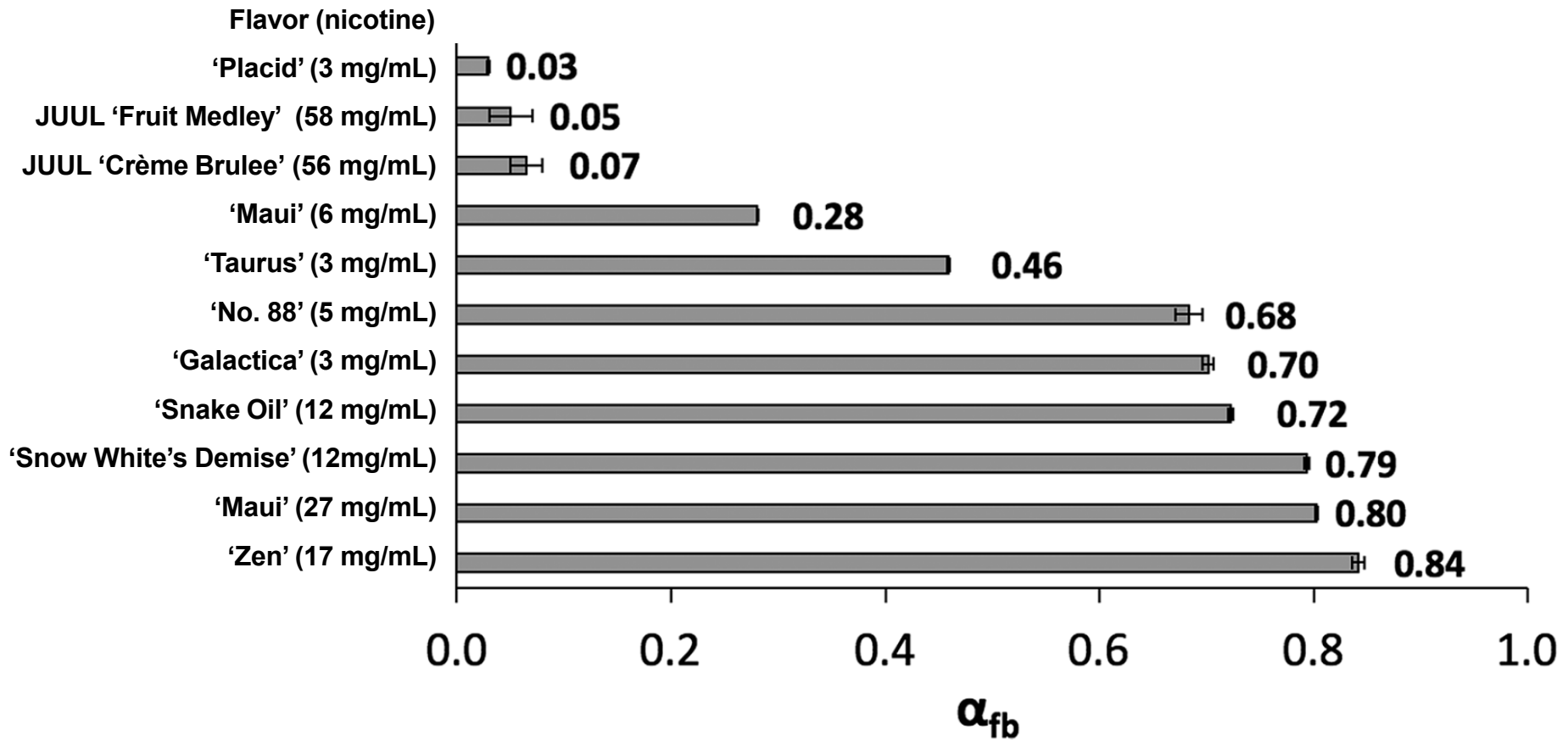
Error Bars  $\pm$  2SE



## Nicotine Chemical Forms Free Base and Protonated (Salt)

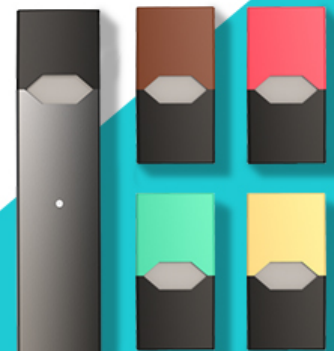


# Free Base Nicotine Fraction in Commercial E-liquids



# Clinical Pharmacology of JUUL Summary

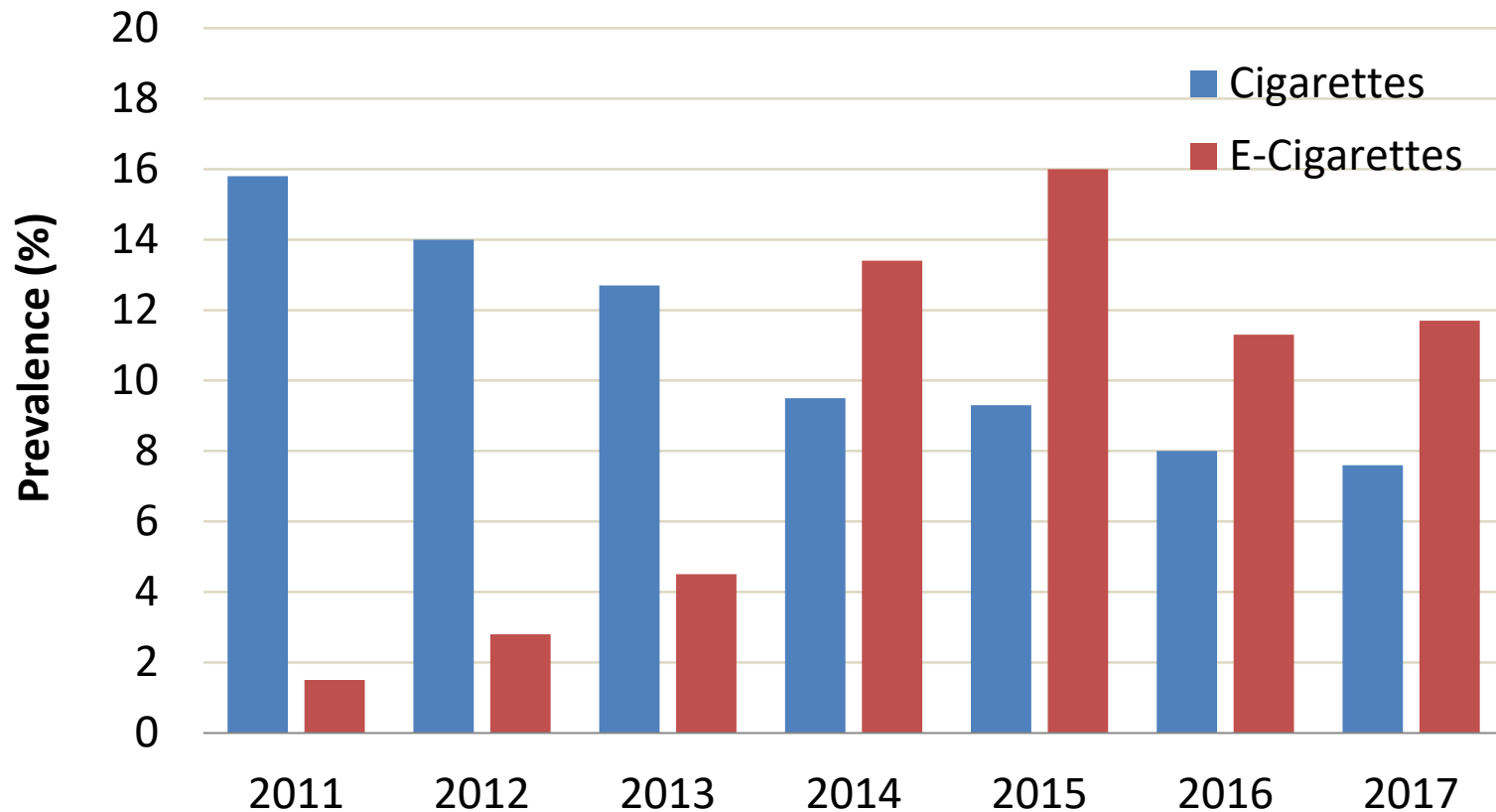
- High concentration of nicotine as benzoate salt
- Easy to inhale high nicotine aerosol due to low pH
- Temperature control reduces generation of thermal degradation products
- Small inhaled volumes along with temperature control reduces toxicant exposure
- Reports of daily use and use for pharmacologic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



# **Are E-cigarettes Harming Youth?**

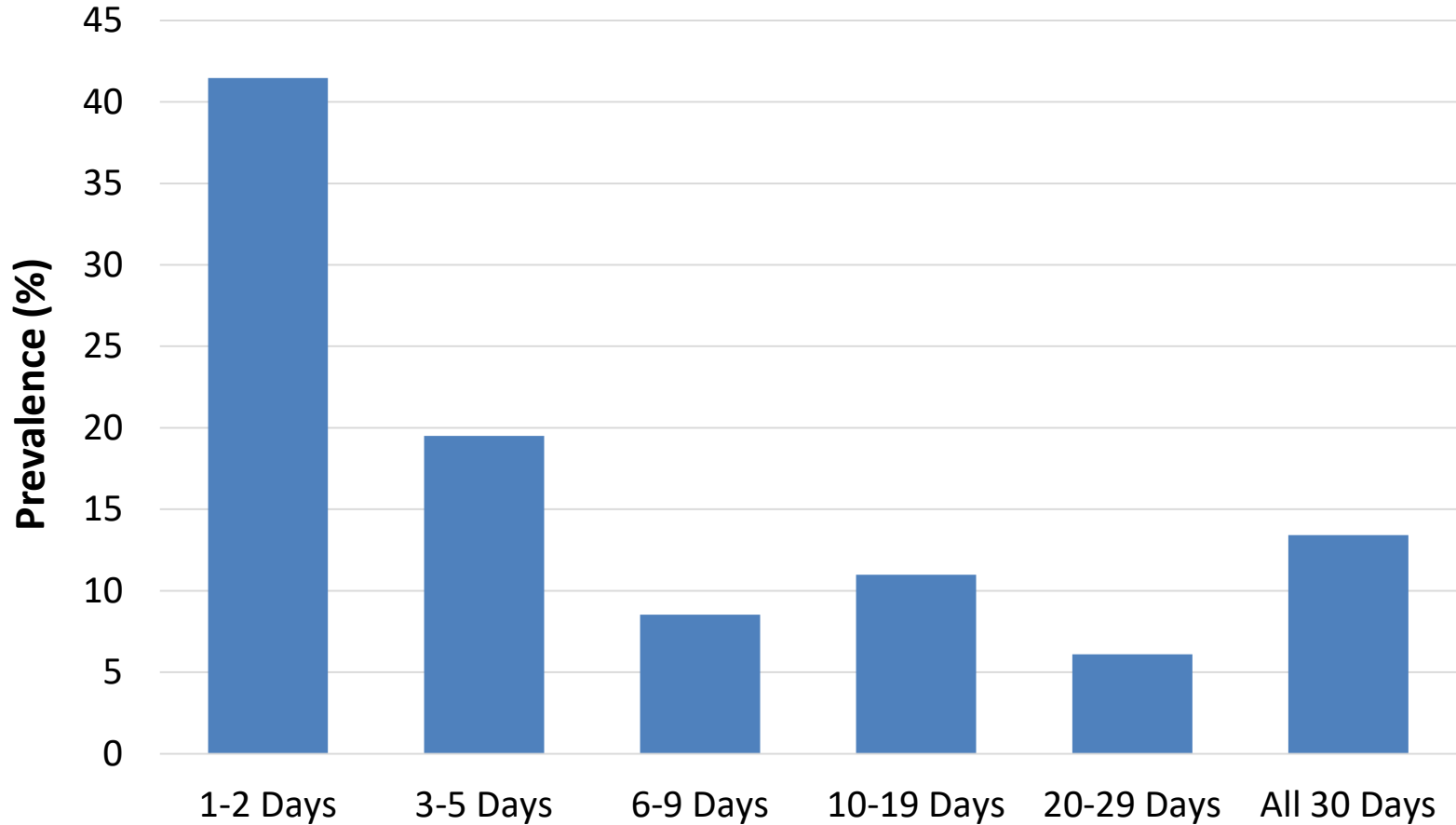
# National Youth Tobacco Survey

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



# National Youth Tobacco Survey

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



THE WALL STREET JOURNAL

# 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.

# The New York Times



## Catching a Ride On the Juul Wave

Kids will keep Juuling until we make vaping as uncool as smoking. Is the Juul craze almost over? Probably not!

**By Amos Barshad**

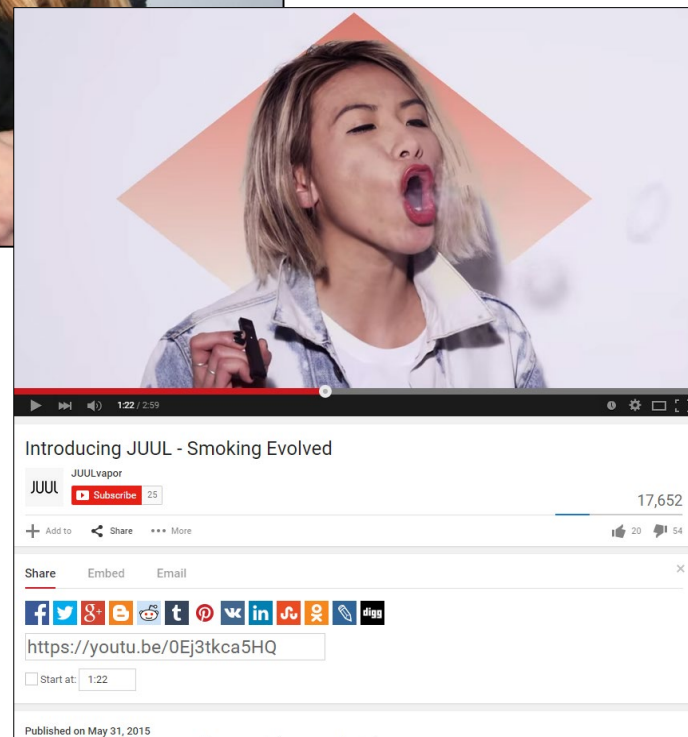
April 7, 2018

*“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!!

liiraven Love the look

priscillathecreator I love his shot of you

cosmicchristine Love this look and going to try this out



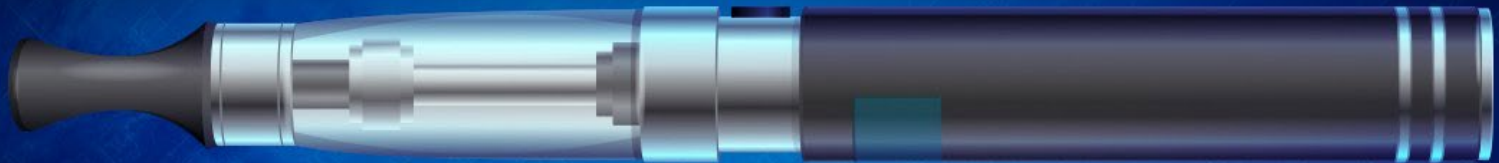
1,515 likes

NOVEMBER 13, 2017

Add a comment...



## 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

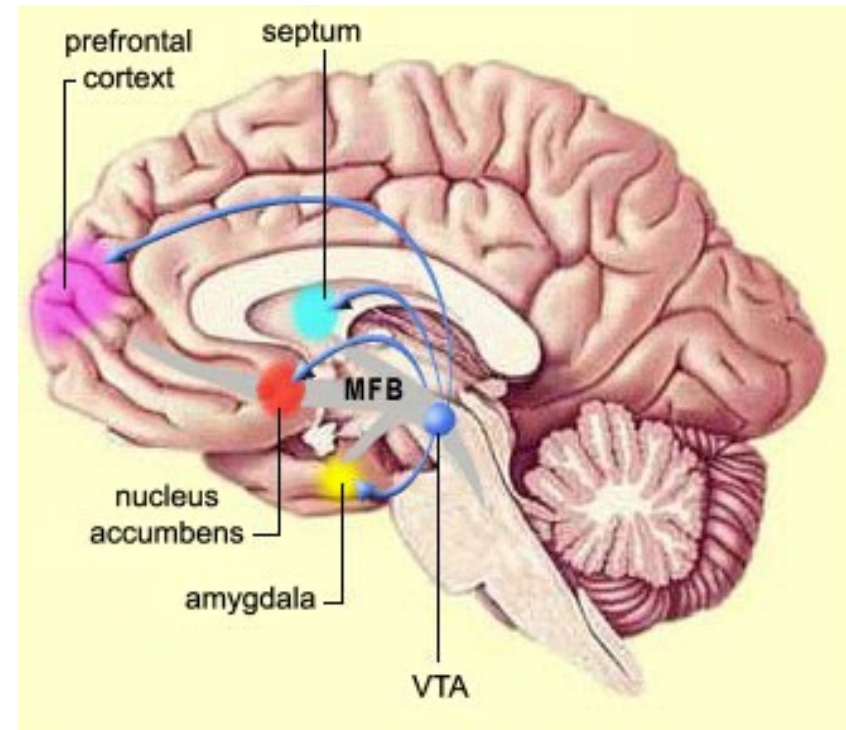
Vaping continues to be associated with smoking. Regular use of e-cigs remains very low among never smokers (**0.2% of 11-18 year olds in 2018**)

# **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.

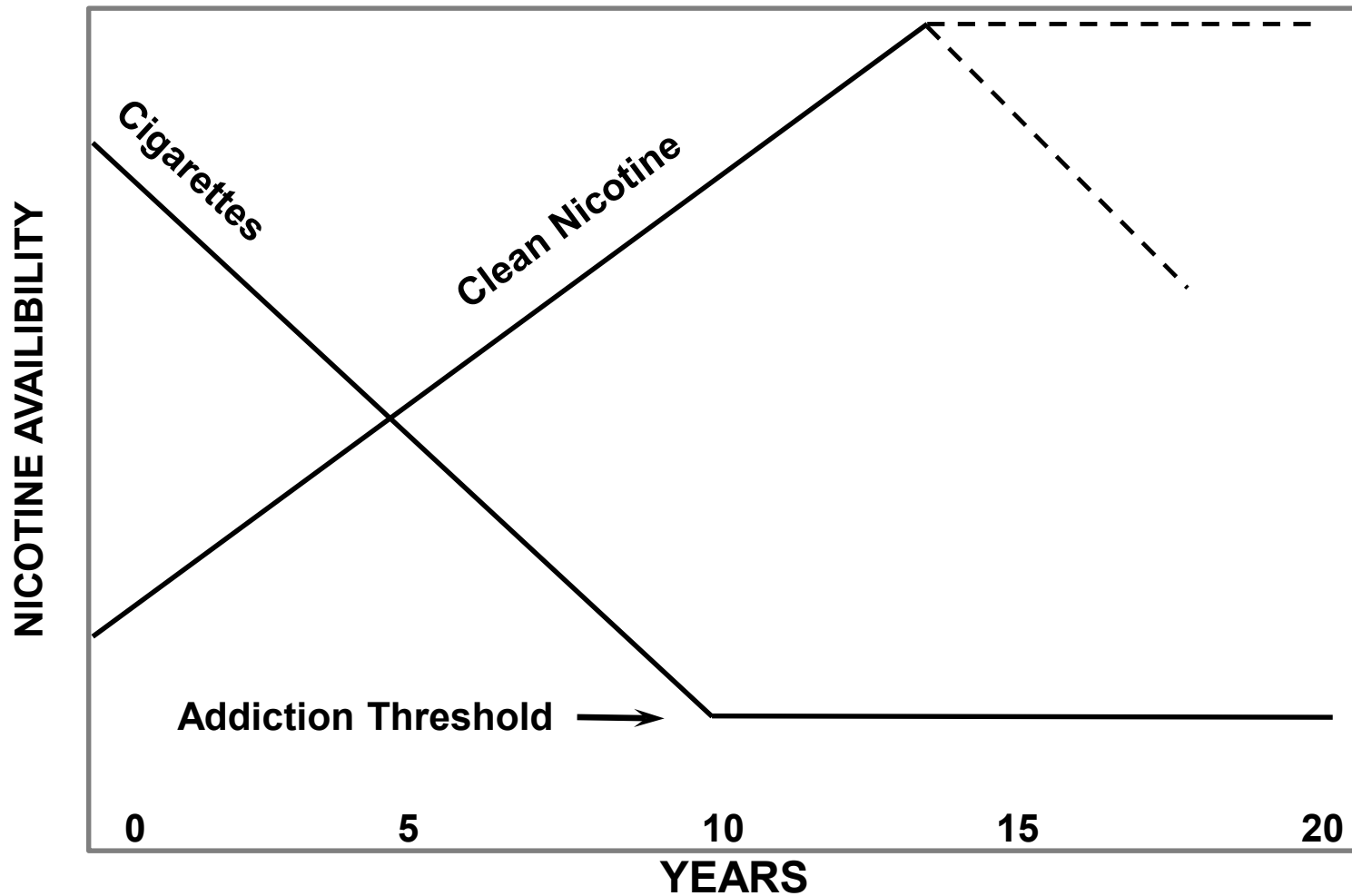


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JOURNAL of MEDICINE

Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. (1994) *N Engl J Med*, 331(2), 123-125.

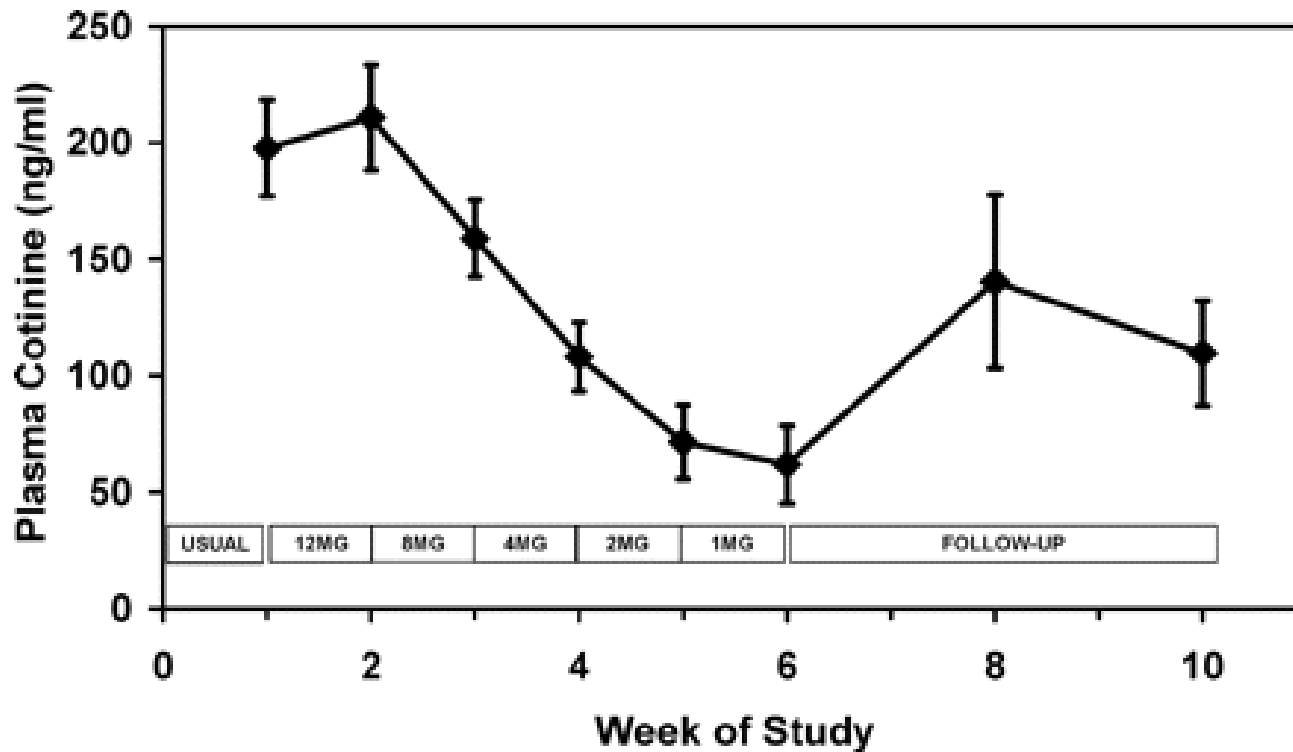


# Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy



**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.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

## 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

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# Preventive Medicine

## 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

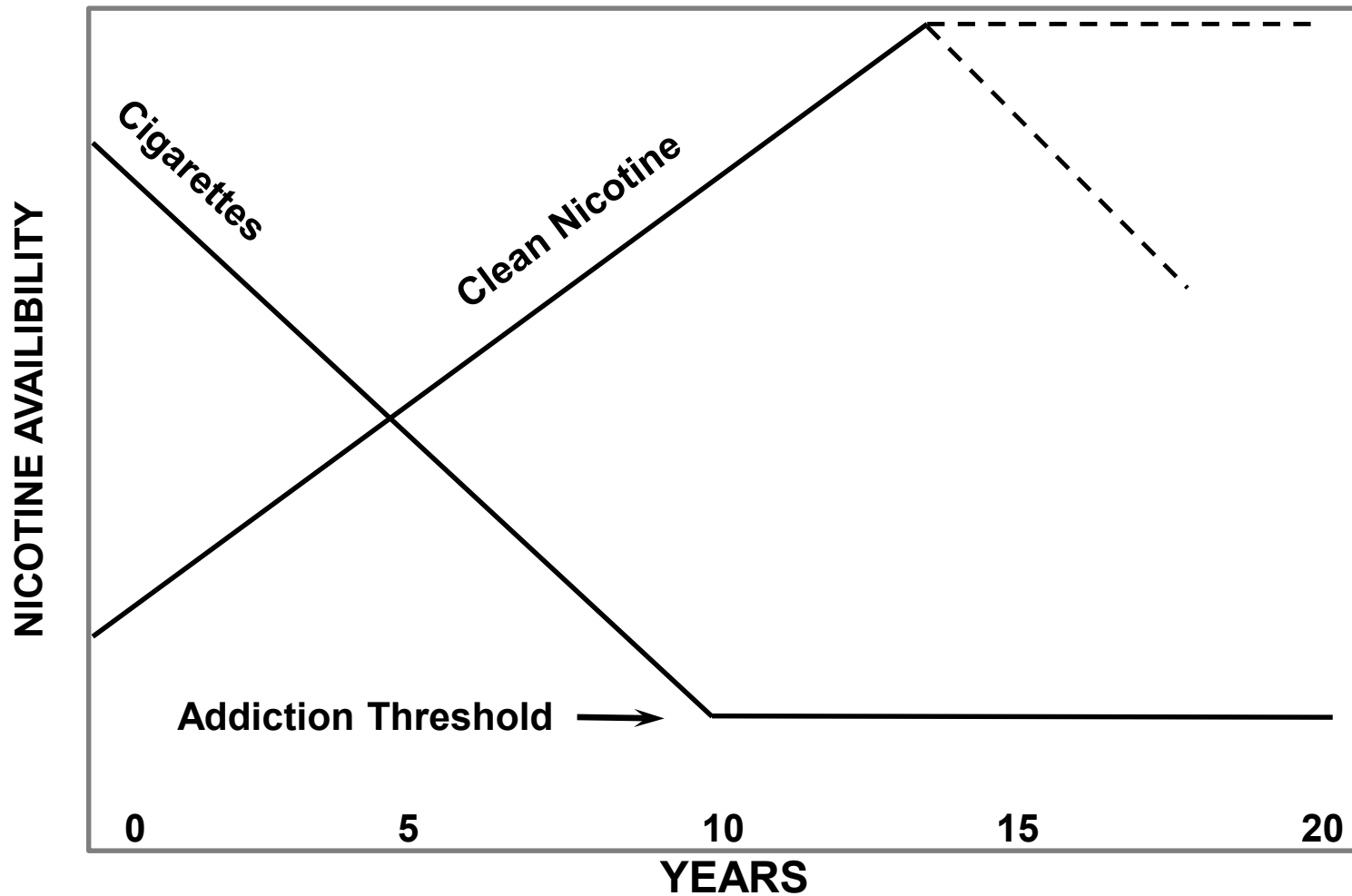
Smoking prevalence likely to decline to 5%, with resultant gain of 137 million QALYs over 50 years

- “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



# 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

