
Smoking Cessation
Leadership Center



University of California
San Francisco

A Comprehensive Look at the Health Effects of Nicotine

Neal L. Benowitz, MD

12/12/19

Moderator

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University of California, San Francisco

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Disclosures

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- Please **make sure your speakers are on** and adjust the volume accordingly.
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- **This webinar is being recorded** and will be available on SCLC's website, along with the slides.
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The University of California, San Francisco (UCSF) School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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This webinar is accredited through the CAMFT for up to **1.0 CEU** for the following eligible California providers:

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For our CA residents, we are working in CA helping behavioral health organizations go tobacco free and integrating cessation services into existing services thanks to the support of the CTCP.

Free CME/CEUs will be available for all eligible California providers, who joined this live activity. You will receive a separate post-webinar email with instructions to claim credit.

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Tips® Campaign Overview

A TIP ABOUT SECONDHAND SMOKE

LET FUTURE GENERATIONS KNOW THE DANGERS OF SECONDHAND SMOKE.

Nathan, Age 54
Ogala Sioux
Idaho

Secondhand smoke at work triggered Nathan's severe asthma attacks and caused infections and lung damage. If you or someone you know wants free help to quit smoking, call 1-800-QUIT-NOW.

#CDCTips

A TIP FROM A FORMER SMOKER

It's easier to move forward when you're not short of breath.

Rebecca, age 57, Florida

Et qui non est, non sitasiam niffa ga arf
Vid qui molate non param, volokna, actio,
sils consuet essevidat laboratibz quanto.
Enant, et ad voler disremped maion faga samam.
Pabiamz atq; saetar; vento quocidatem nitrooz.
You can quit.

CALL 1-800-QUIT-NOW.

#CDCTips

A TIP FROM A FORMER SMOKER

BE CAREFUL NOT TO CUT YOUR STOMA.

Shawn, Age 50, Diagnosed at 46
Washington State

Smoking causes immediate damage to your body. For Shawn, it caused throat cancer. You can quit. For free help, call 1-800-QUIT-NOW.

1. CDC. Current Cigarette Smoking Among Adults—United States, 2005–2014.. MMWR 2015;64(44):1233–40
2. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: HHS,CDC, NCCDPHP, OSH, 2014

Free 1-800 QUIT NOW cards

Take Control
1-800-QUIT-NOW
Call. It's free. It works.
1-800-784-8669
For details on your state services, go to: <http://map.naquitline.org>



- ✓ Refer your clients to cessation services

Presenter

Neal L. Benowitz, MD

Emeritus Professor of Medicine and
Bioengineering & Therapeutic Sciences

University of California, San Francisco



UCSF Center for Tobacco Control
Research and Education

Harms and Risks of Nicotine: Implications for Tobacco Harm Reduction

Neal L Benowitz MD

University of California San Francisco

Smoking Cessation Leadership Center
Webinar

December 12, 2019



Disclosures

Dr. Benowitz has been a consultant to pharmaceutical companies that market smoking cessation products, including Pfizer and Achieve Life Sciences and a paid expert in litigation against tobacco companies

The Question

- The harms and risks of nicotine are an essential consideration in assessing the public health impact of nicotine-based harm reduction.
- What do we know about the safety of long-term use of nicotine delivered without tobacco combustion?

Some Nicotine-related Clinical Concerns

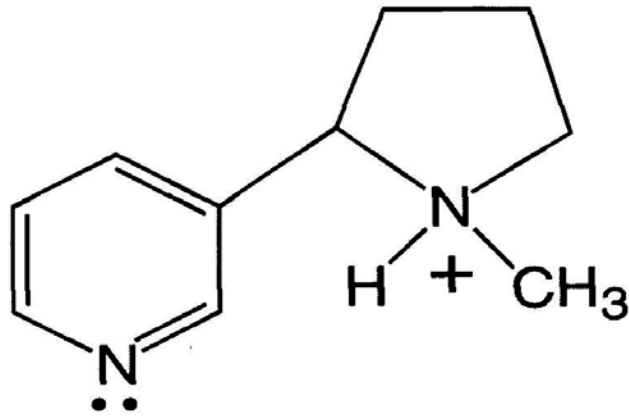
- Should the vaper who has switched from cigarette smoking to e-cigarettes be counseled to quit vaping?
- What are the health risks of primary nicotine addiction in never-smokers?

Brief Summary

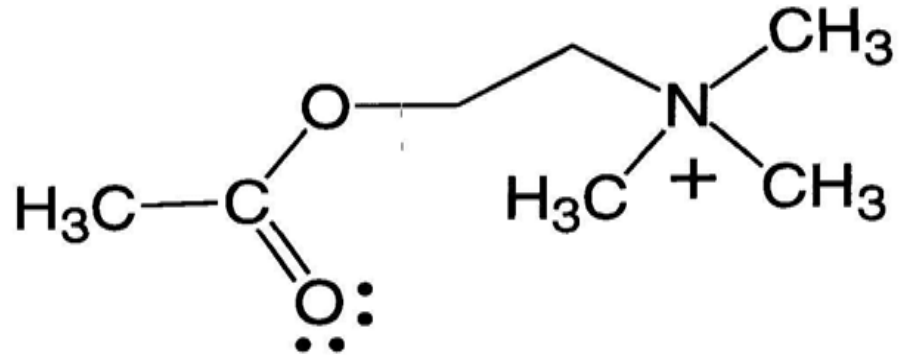
- Nicotine has effects on every part of the body, and basic research suggests many potential harms
- Long term nicotine use, while not harmless, is much less harmful than cigarette smoking
- The harms of long term inhalation of nicotine without tobacco combustion have not been determined and need to be studied
- The acceptability of nicotine addiction per se in non-smokers is both a health and socio-cultural question

Pharmacologic Mechanisms

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

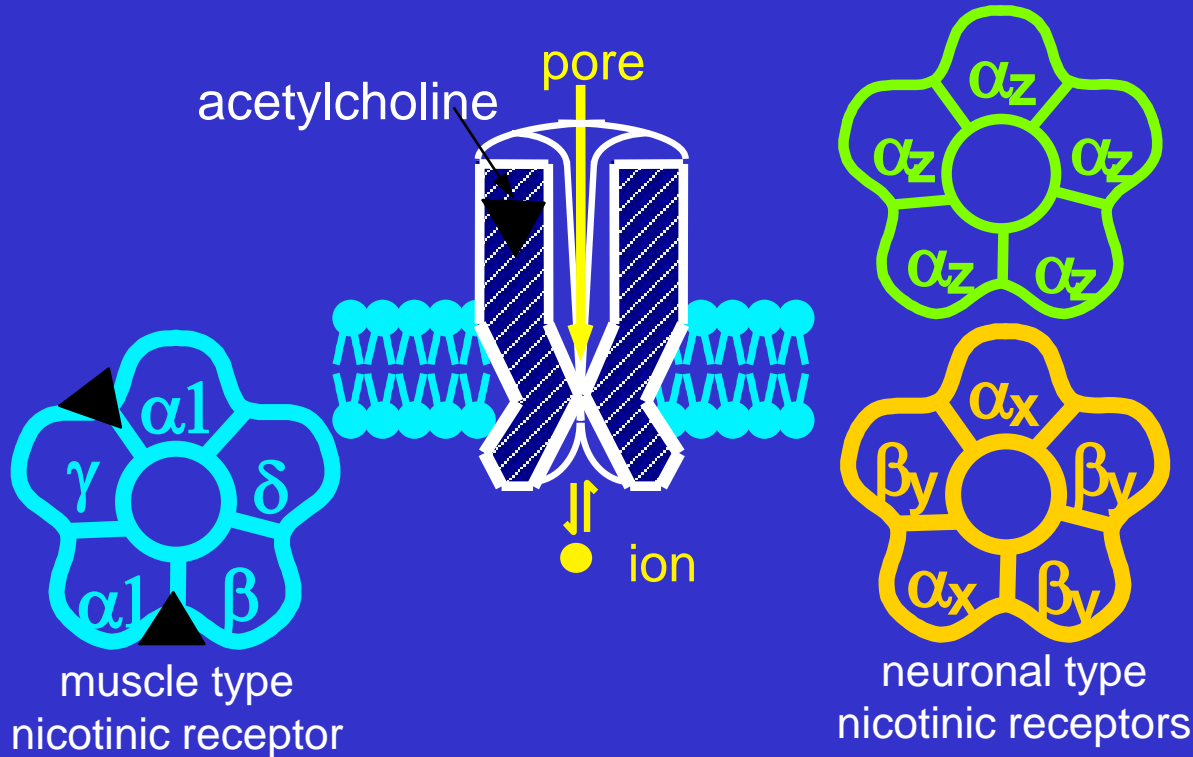


NICOTINE



ACETYLCHOLINE

Structure of Nicotinic ACh Receptors



Pharmacologic mechanisms by which nicotine might cause harm

NAChR subtype

- $\alpha4\beta2^*$
- $\alpha3\beta4$
- $\alpha7$ homomeric

Effects

- Dopamine release, addiction, neuroplasticity
- Sympathetic stimulation, catecholamine release, CV toxicity
- Endothelial dysfunction, angiogenesis, inhibition of apoptosis, anti-inflammation

Caveat regarding in vitro studies-normal homeostatic mechanisms not operative

Pharmacologic Effects of Nicotine

- Facilitates neurotransmitter release
(e.g. dopamine)
- Sympathetic neural stimulation
- Immune suppression
- Oxidant stress
- Endothelial dysfunction
- Inhibition of apoptosis
- Promotes cell growth, including angiogenesis

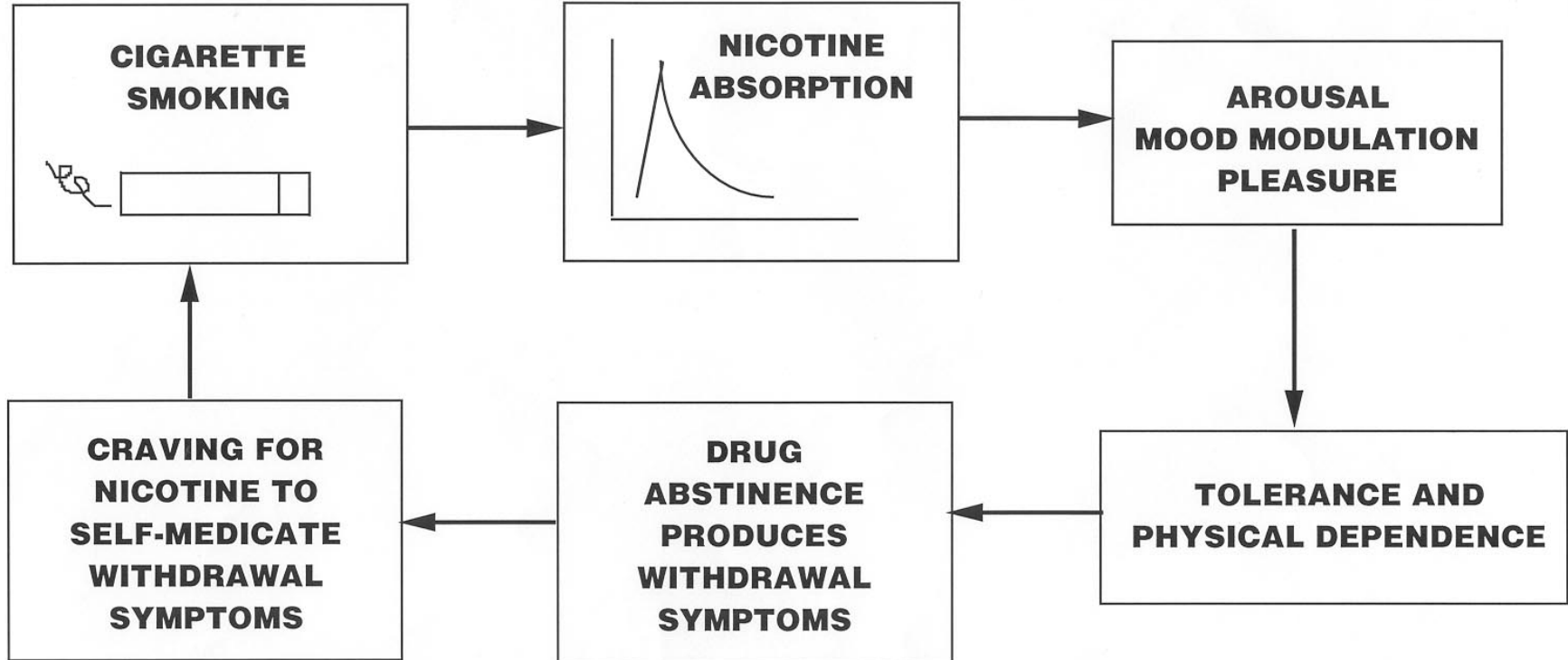
Major Safety Concerns for Nicotine

- **Addiction**
- Cardiovascular disease
- Reproductive Toxicity
- **Impaired Adolescent Brain development**
- **Infectious Disease Risk**
- **Cancer**
- **COPD**
- **Definite**
- Probable
- Probable
- **Possible**
- **Possible**
- **Possible**
- **Unlikely**

Nicotine and Addiction

- Nicotine essential for tobacco addiction, but other factors enhance addictiveness
- Speed of nicotine delivery to brain is a key determinant
- Pattern of nicotine dosing and potential for addiction varies by delivery device

NICOTINE ADDICTION CYCLE



Nicotine intake from cigarette smoking

- Typical systemic nicotine intake 1 to 1.5 mg per cig; can vary from 0 to 4 mg
- Regular daily smoking of 15 cpd corresponds to 15 to 22 mg nicotine per day
- Corresponding cotinine levels 120 to 180 ng/ml

Daily Nicotine Exposure with various Nicotine Delivery Systems

- Swedish snus users and former smokers who use ECig only have similar cotinine levels to typical cigarette smokers
- Experimental switching studies – ECig users can achieve similar nicotine intake to when smoking
- Titration of nicotine intake seen across ECig products

E-Liquid nicotine concentrations do not predict daily nicotine exposure



**Nicotine
Concentration**

**Blood/saliva
Cotinine**

4.1 mg/ml

430 ng/ml

22.5 mg/ml

316 ng/ml

59 mg/ml

172 ng/ml
(50 – 313)

Nicotine in E-cigarettes

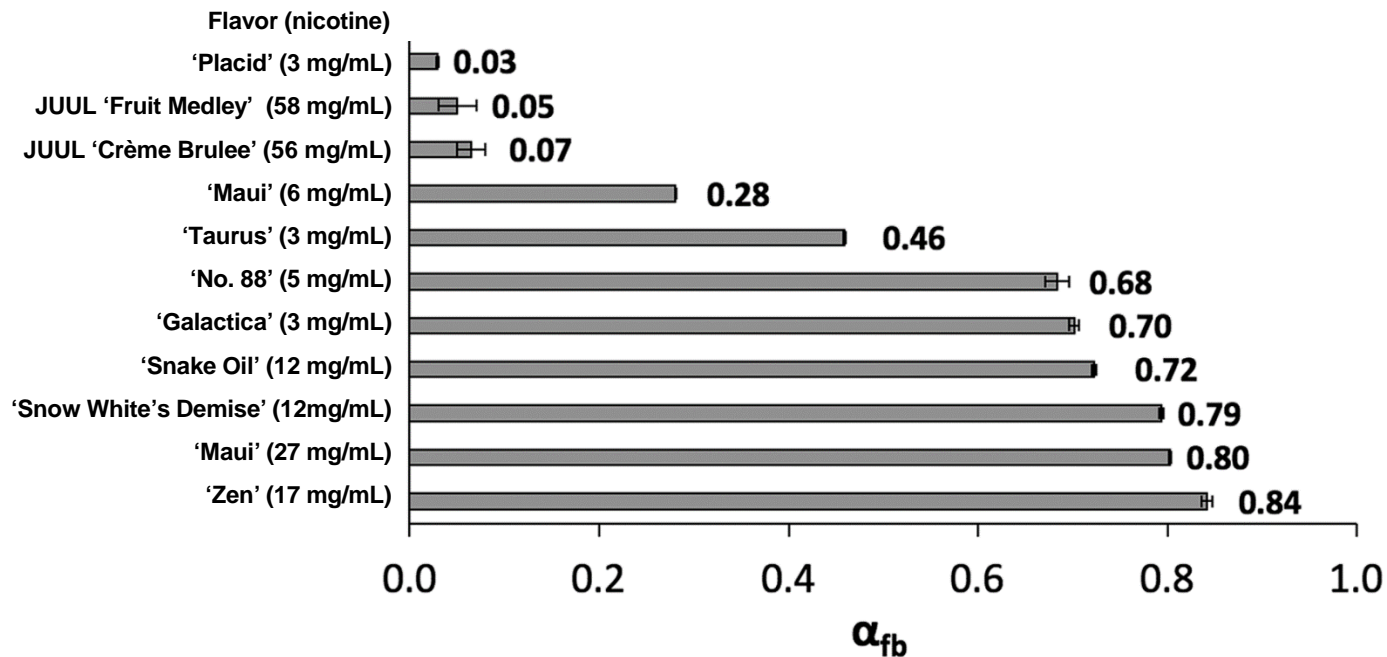
- Nicotine levels in E-liquids vary from 0 to 100 mg/ml.
- Nicotine delivery depends on temperature of coil, nicotine content of liquid and PG/VG ratio
- Higher nicotine concentration results in high pH. Nicotine salts result in lower pH.
- pH of liquid may influence sensory characteristics, site of nicotine absorption and absorption rate

Characterization of Nicotine Salts in 23 E-cigarette Refill Liquids

(Harvanko et al, under review)

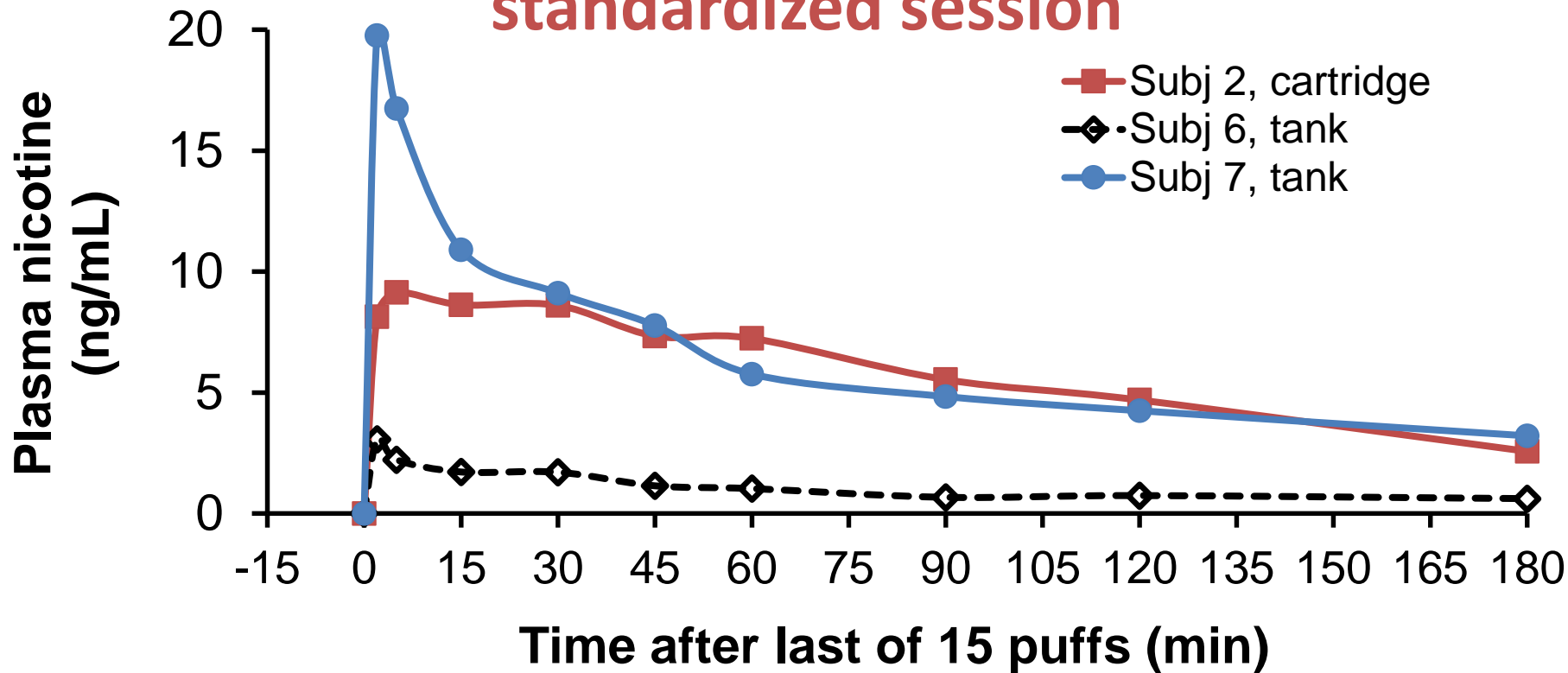
- Salts: lactic (11), benzoic (8), levulinic (4), salicylic (2), malic (2), tartaric (1), unkn (1)
- 3 liquids contained multiple salts
- Nicotine avg 45, range 20 to 89 mg/ml
- pH avg 4.9, range 3.5 to 6.8

Free Base Nicotine Fraction in Commercial E-liquids

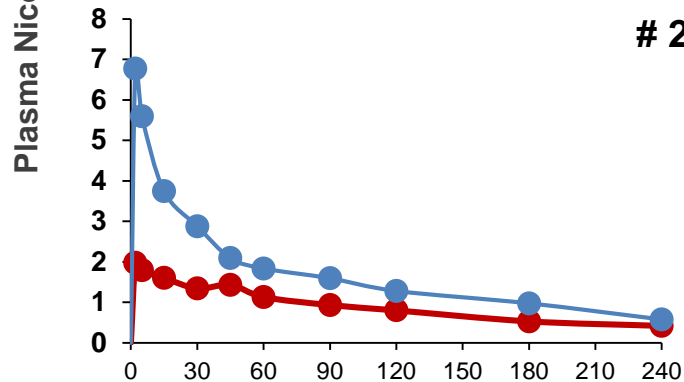
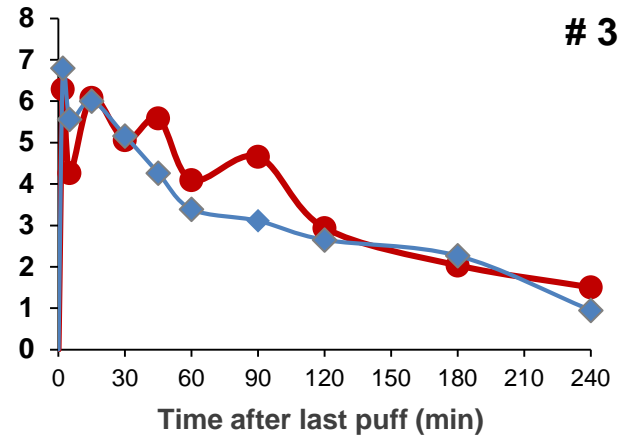
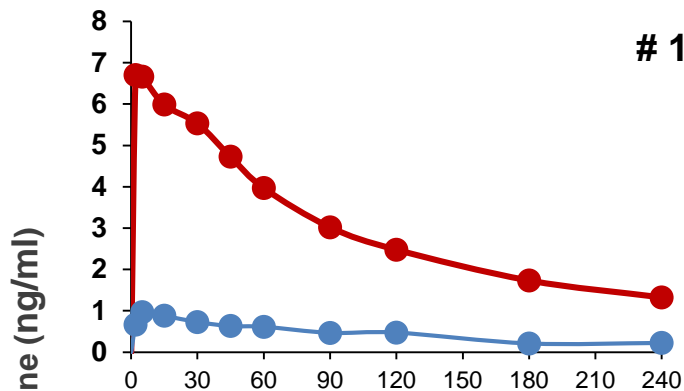


**Nicotine pharmacokinetic
profile differs by delivery
system –
could have implications for
addiction and other toxicity**

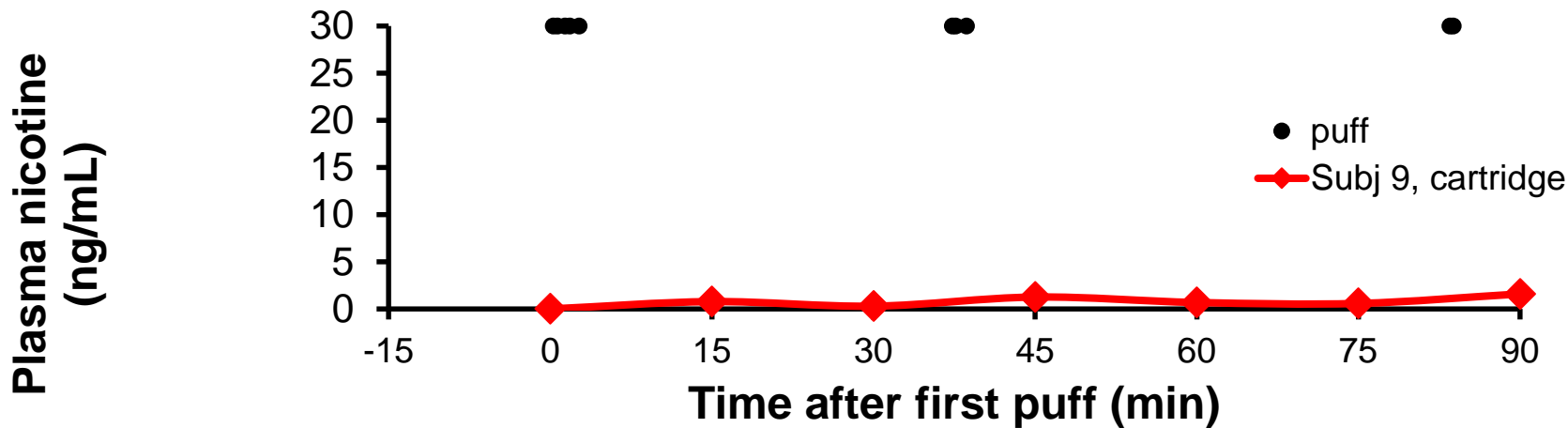
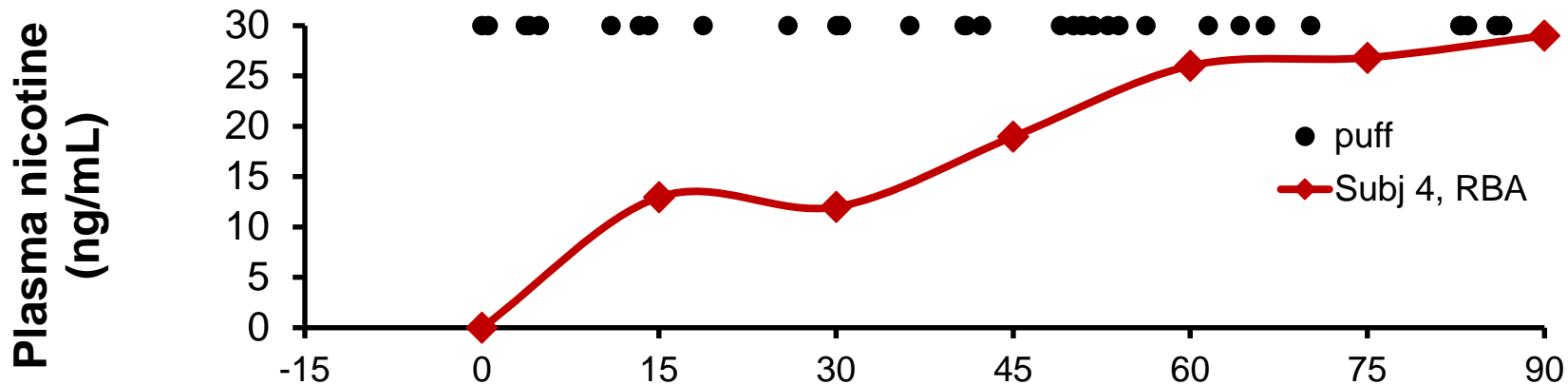
Nicotine PK with E-cigarette use during standardized session



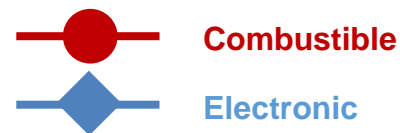
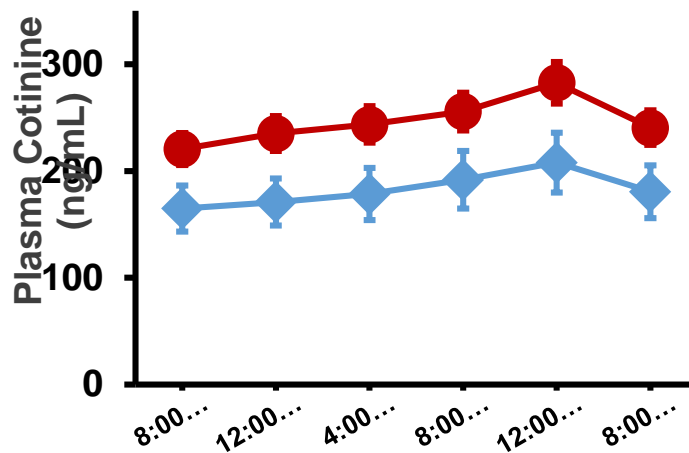
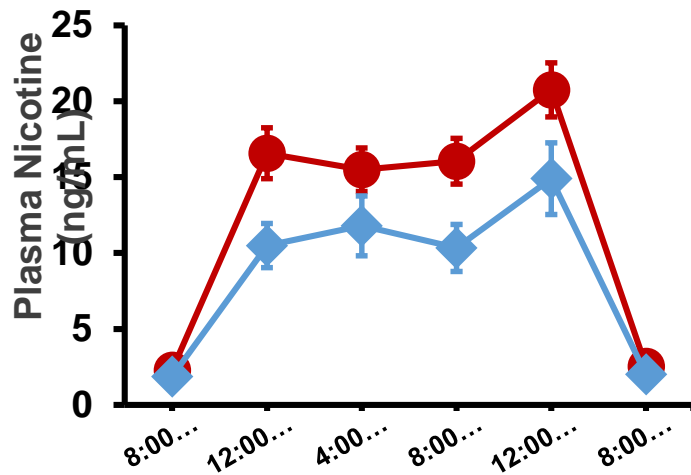
Nicotine Pharmacokinetics Comparing Cigarettes to JUUL



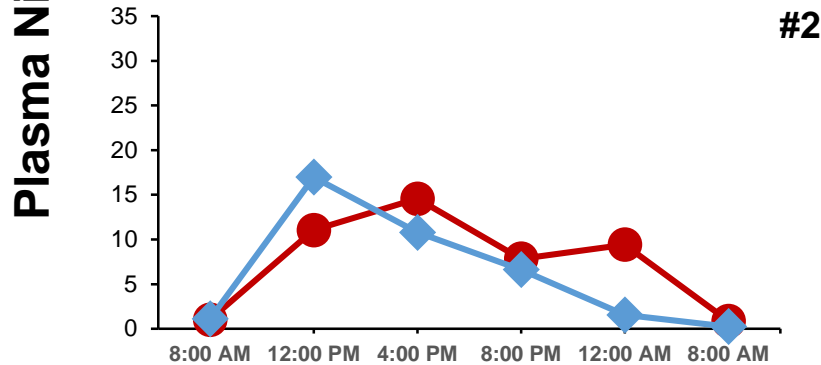
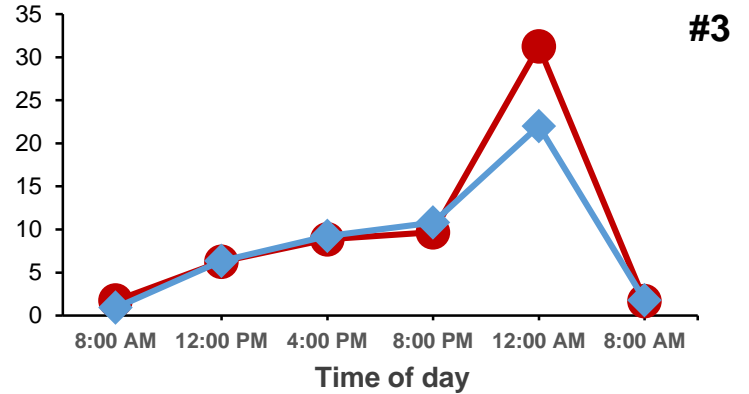
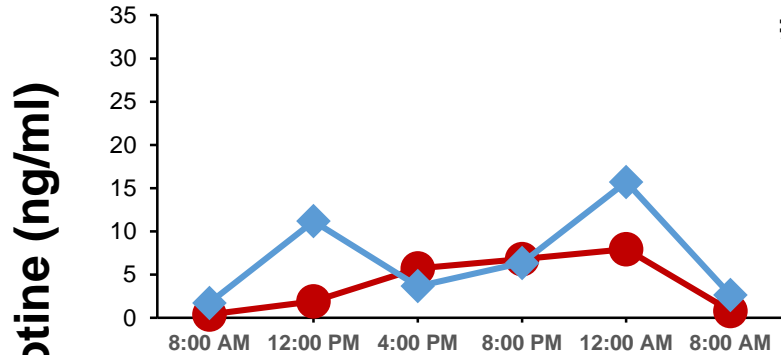
Nicotine PK with ad libitum E-cigarette use



Circadian Plasma Nicotine and Cotinine Concentrations with ad lib smoking and vaping (N=36), UCSF



Circadian Plasma Nicotine While Smoking Cigarettes or JUULing in Dual Users

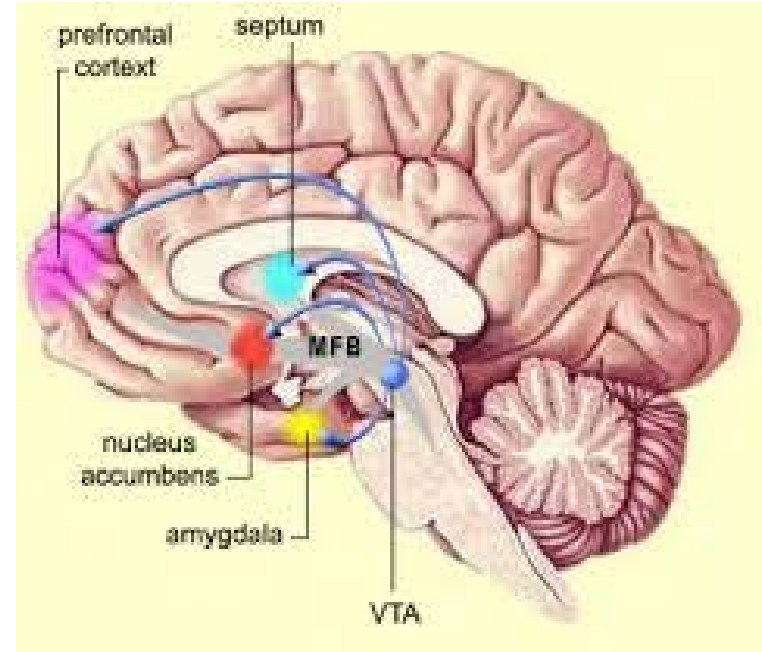


Nicotine and Adolescent Brain Development

**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: decision making, impulse control and executive function



Nicotine has effects on adolescent rat brain that persist into adulthood

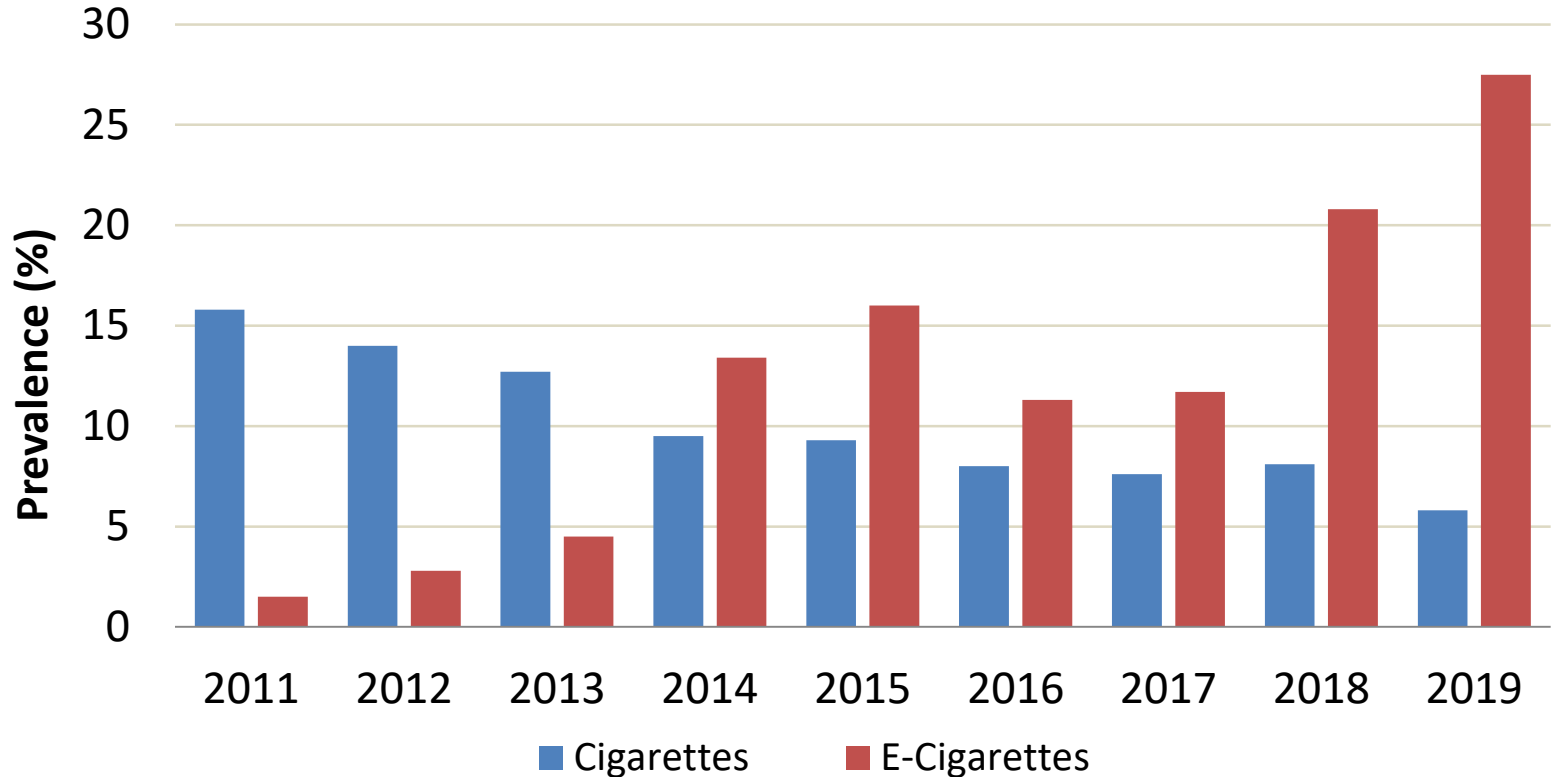
- Delayed maturation of prefrontal cortex
- Persistent changes in dopamine release
- Anxiogenic phenotype in adulthood
- Persistent deficit in cognitive function
- Greater rewarding effects of drugs of abuse.
Enhanced acquisition of nicotine and cocaine self-administration in adulthood

Caveats in interpreting human causation

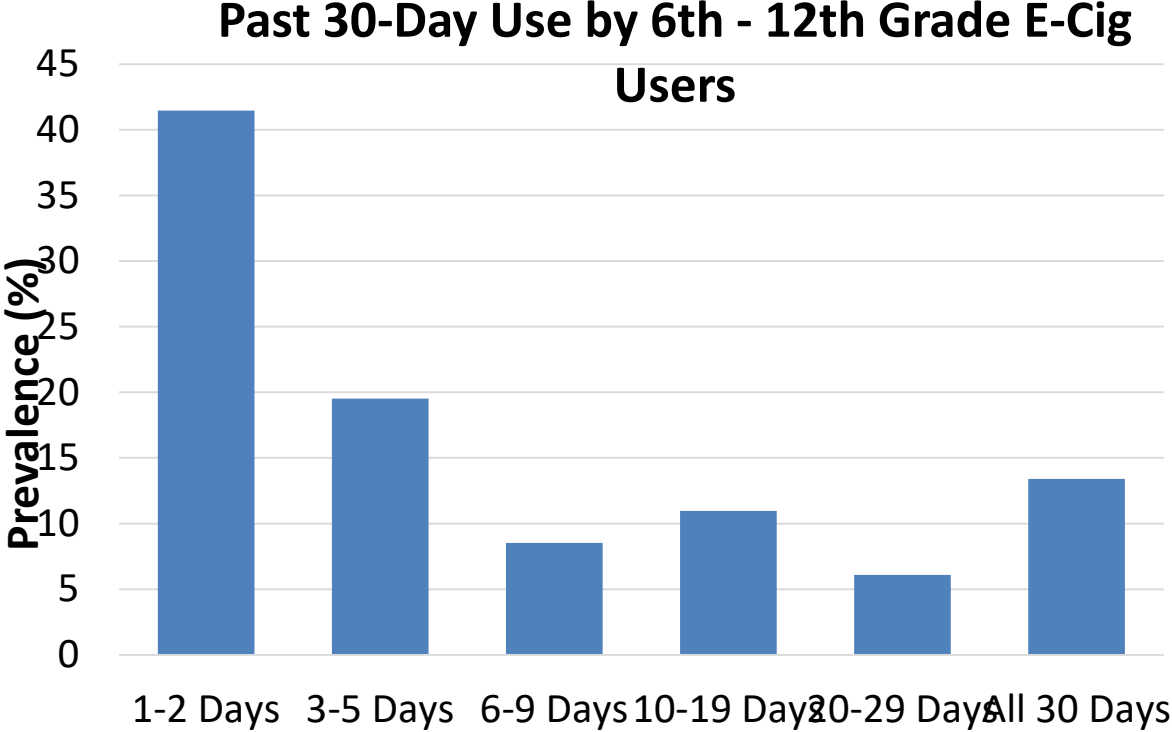
- Most data on nicotine and brain development from studies in rats
- In people, difficult to distinguish effects of nicotine/tobacco from genetic and social environmental influences

National Youth Tobacco Survey

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

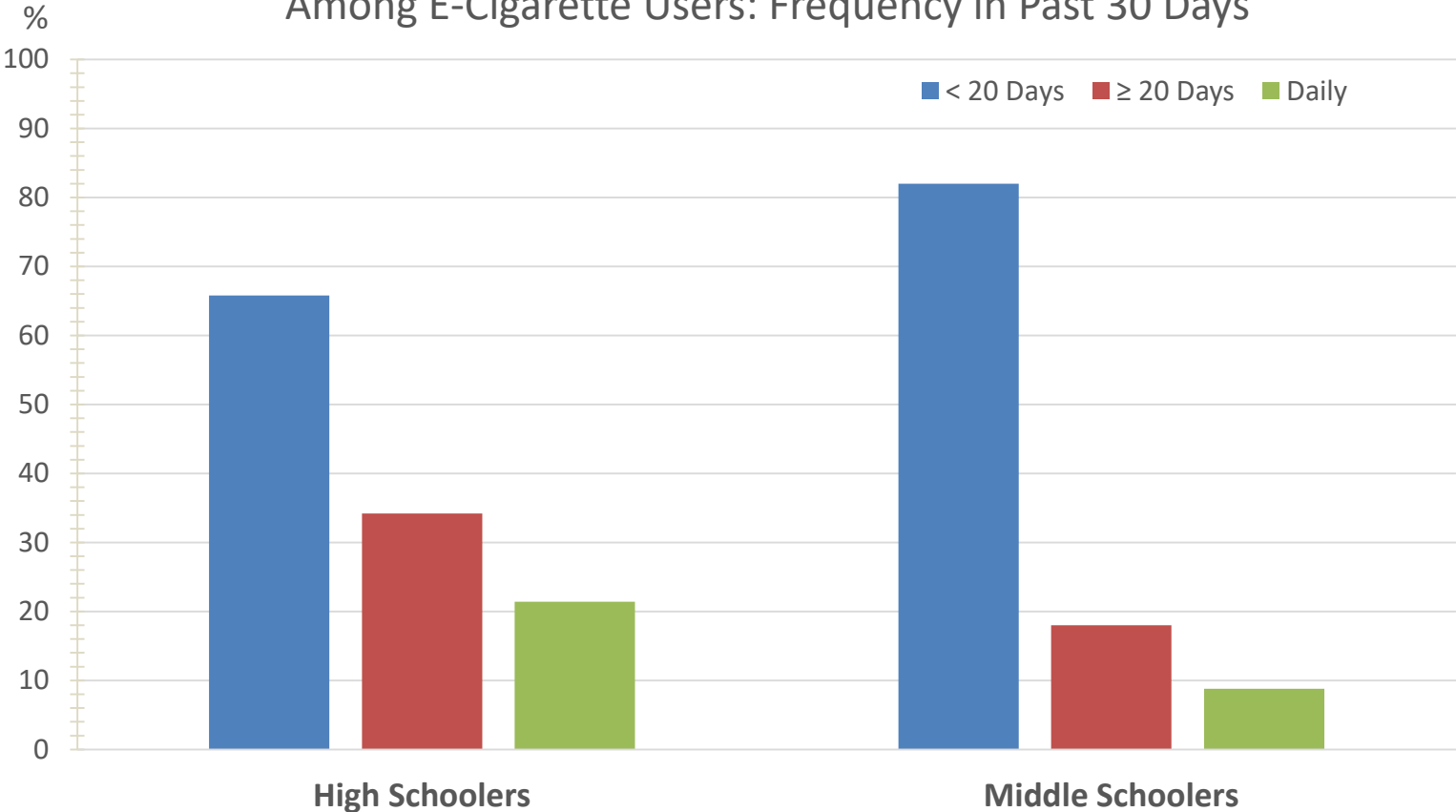


National Youth Tobacco Survey - 2017



National Youth Tobacco Survey - 2019

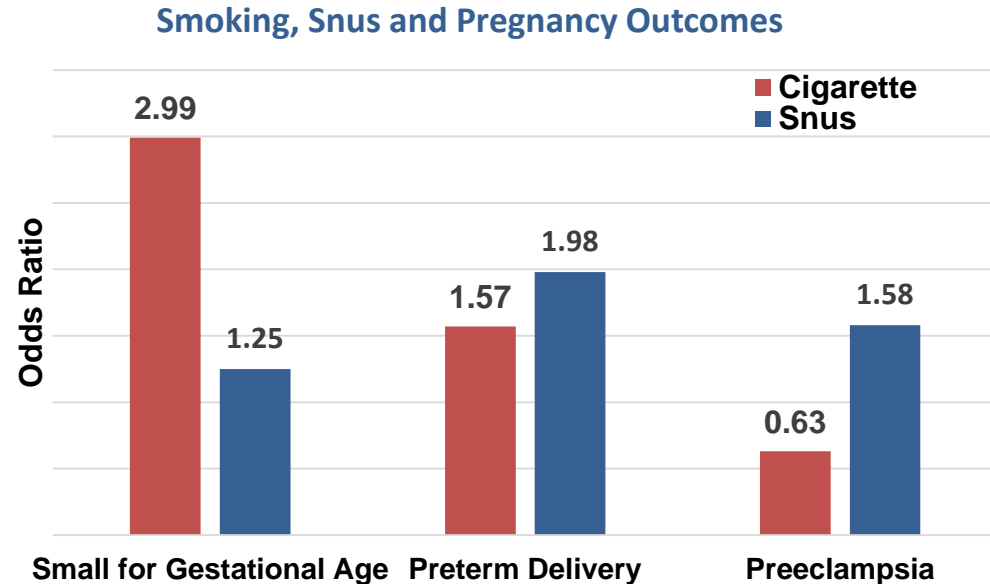
Among E-Cigarette Users: Frequency in Past 30 Days



Reproductive Toxicity of Nicotine

Reproductive Toxicity of Nicotine

- Fetal neuroteratogenesis
- Impaired neonatal lung development
- Adverse effects of snus on pregnancy:
 - Low birth weight
 - Pre-term delivery
 - Preeclampsia
 - Spontaneous abortion



Risk of Swedish Snuff Use (Snus) during Pregnancy

7000+ pregnant snus users

	<u>Odds Ratio</u>	<u>95% CI</u>
Stillbirth	1.6	1.1-2.3
Preterm birth	1.38	1.04-1.83
Pre-eclampsia	1.11	0.97-1.28

Wikstrom et al. Epidemiology 21: 772, 2010
BJOG 117: 1005, 2010
Hypertension 55: 1100, 2010

Cardiovascular Safety of Nicotine

Constituents of Tobacco Smoke and EC Aerosol that could contribute to CVD

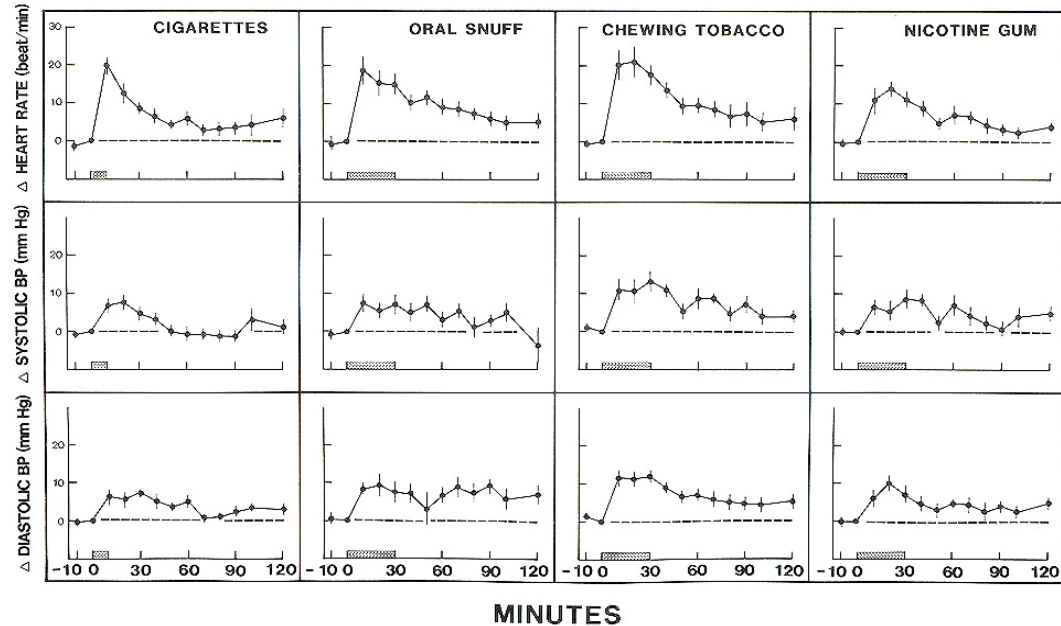
- Oxidizing chemicals #
- Carbon monoxide *
- Volatile organic compounds #
- Particulates
- Heavy metals #
- Nicotine

* Not present in EC aerosol

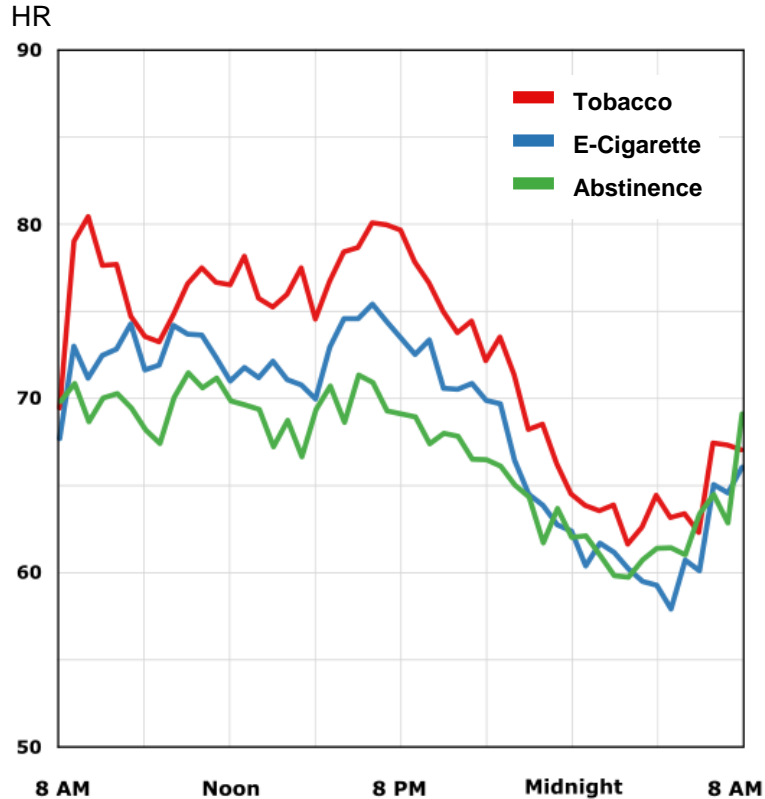
Present at much lower levels

Hemodynamic Effects of Nicotine

- Increased heart rate and BP
- Increased myocardial contractility and myocardial work
- Coronary vasoconstriction & Reduced coronary flow reserve
- Cutaneous vasoconstriction
- Skeletal muscle vasodilation



Circadian Heart Rate Effects of Cigarette Smoking and E-Cigarette Use

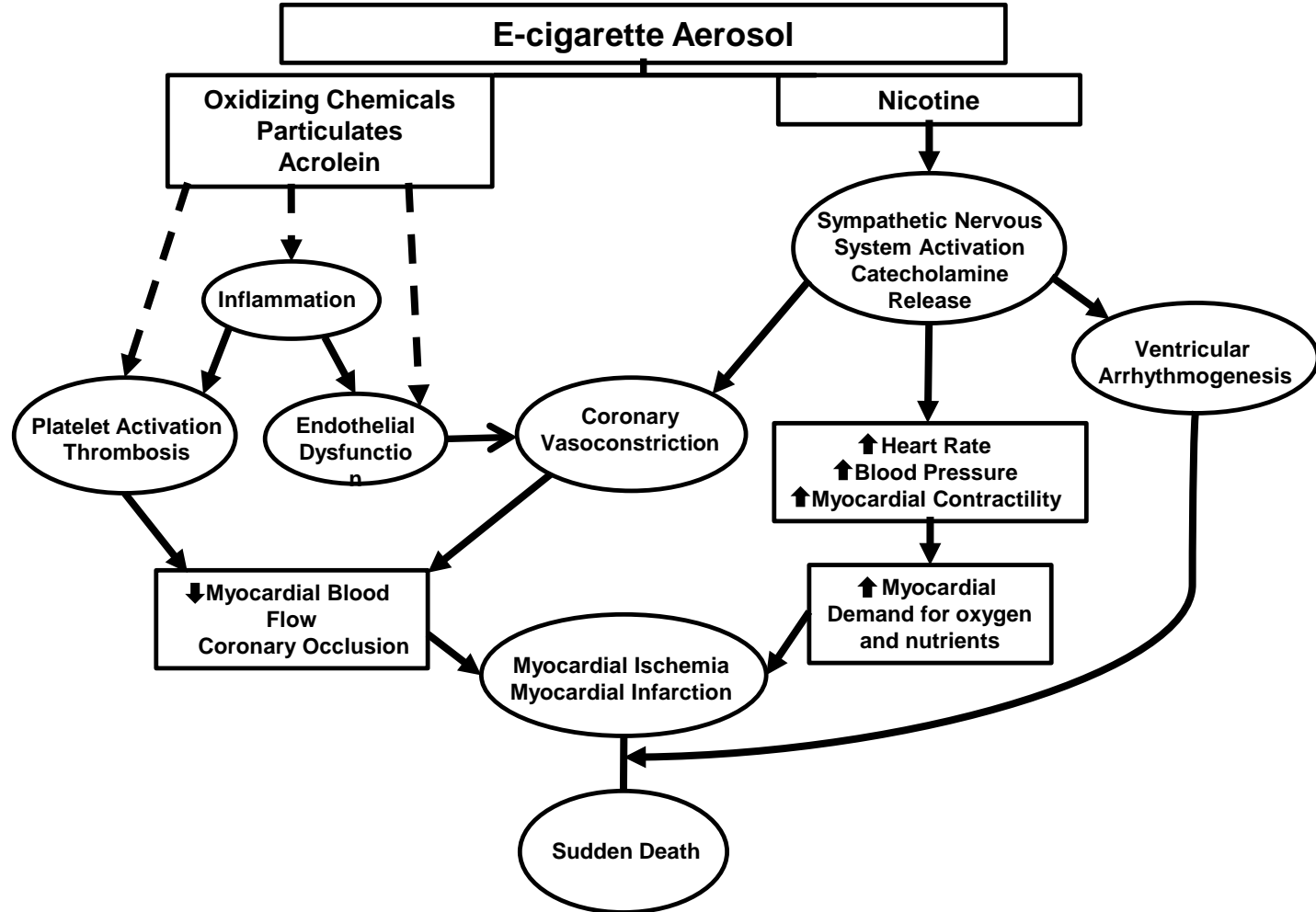


Heart rate acceleration indicates persistent sympathetic neural activation

Other Consequences of Nicotine-induced Sympathetic Neural Activation

- Arrhythmogenesis (risk of sudden cardiac death)
- Lipid abnormalities
- Insulin resistance and diabetes
- Inflammation (splenocardiac axis)

Mechanisms by which E-cigarettes could cause Acute CV Events



Health Effects of Smokeless Tobacco:

Natural Experiment on Effects of Nicotine without Combustion Toxicants

Snus Products



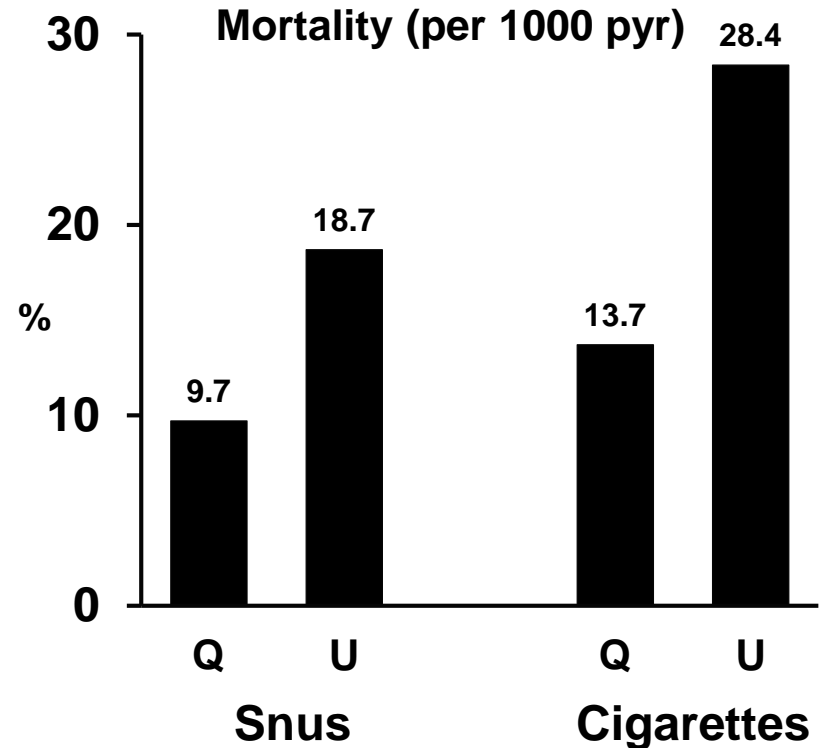
Swedish snus

American snus



Smokeless Tobacco and CVD: Swedish Snus

- Similar daily nicotine exposure, but slower absorption
- No effect on platelet activation or carotid intimal thickness
- Case control studies – no increase in risk of MI or stroke; small but significant increase in case fatality
- Increased mortality with continued snus after MI
- Increased risk of heart failure, but not atrial fibrillation



Conclusions: Nicotine and Cardiovascular Disease

- Biological plausibility and epidemiological evidence that nicotine may contribute to acute CV events
- Short term nicotine use poses little CV risk
- Long term nicotine use may be harmful in the presence of CVD

Nicotine and Respiratory Disease

Nicotine and respiratory disease: possible mechanisms

- Immune suppression
- Promotion of airway and smooth muscle proliferation
- Oxidative stress
- Reduced cough reflex and ciliary function
- Acute lung injury (high dose)
- Impaired in utero lung development
- Emphysema-like changes in rodents

Nicotine and Respiratory Infectious Disease Risk

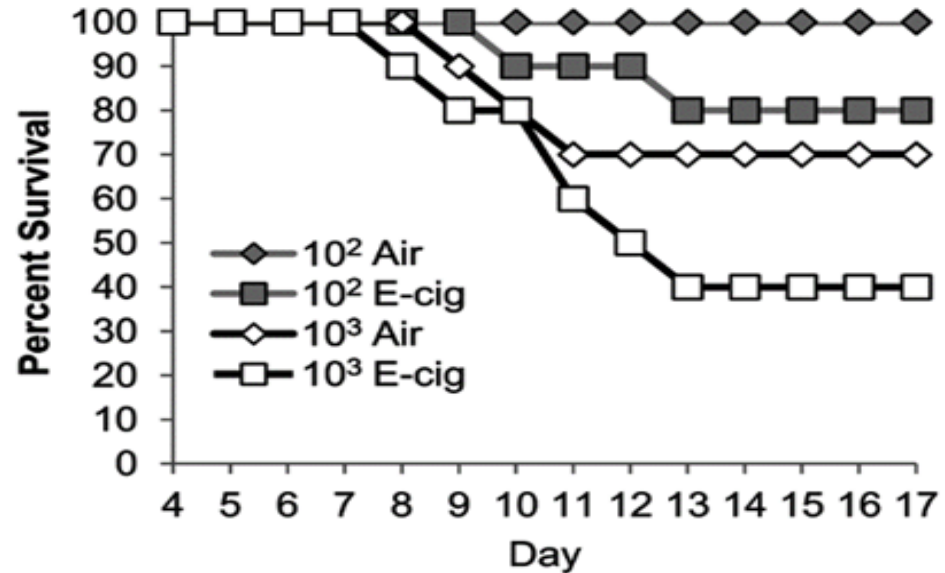
Nicotine cholinergic immunosuppression:

Enhances survival in animal models of immune disease

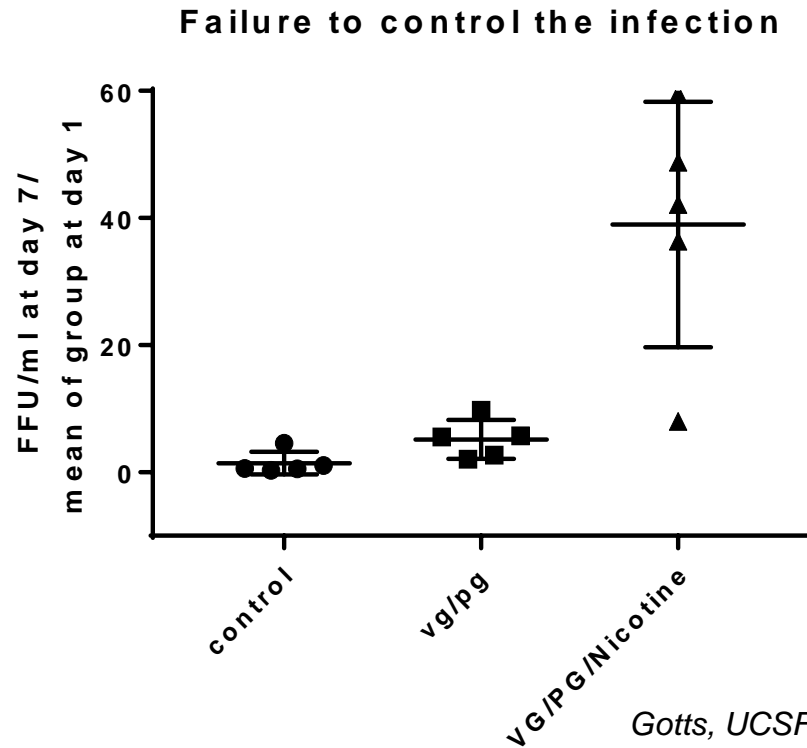
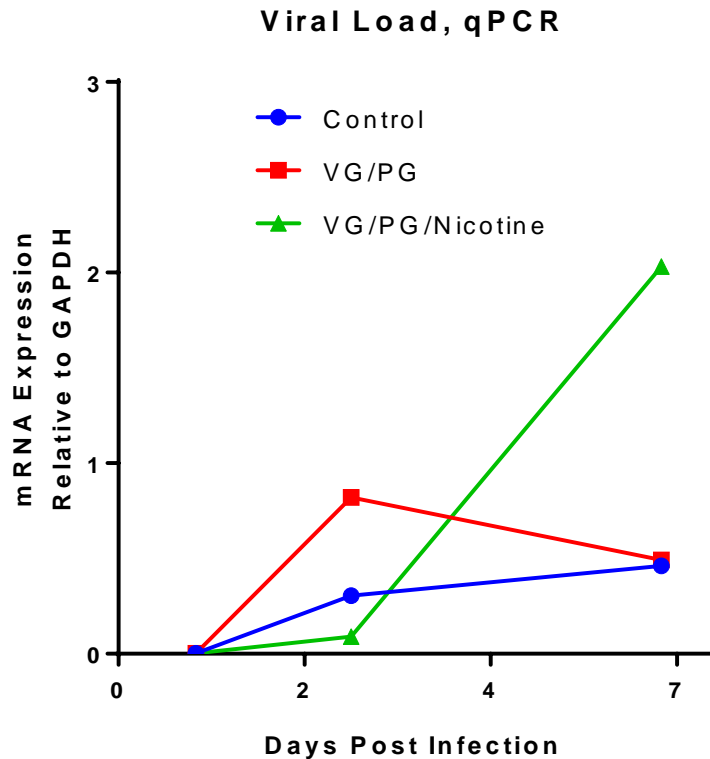
Nasal mRNA changes in Ecig users suggest immune down-regulation

Ecig aerosol increases mortality from respiratory infection in mice

No human epidemiology on nicotine and infection



Nicotine Impairs Clearance of Influenza Virus in Mice

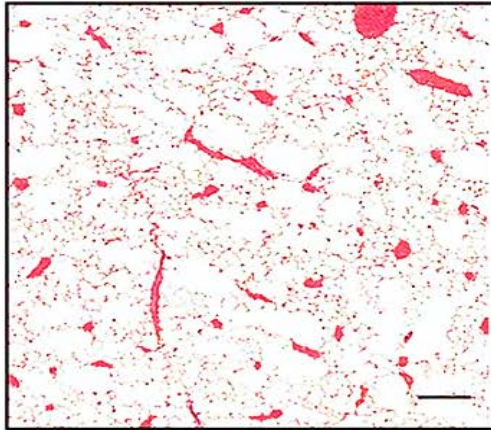


Nicotine and Chronic Lung Disease

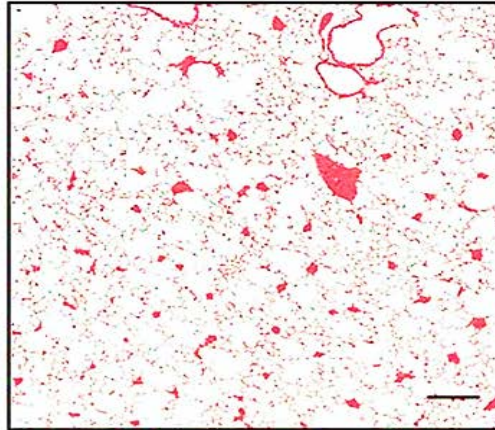
Emphysema-like changes in mice

No human epidemiology

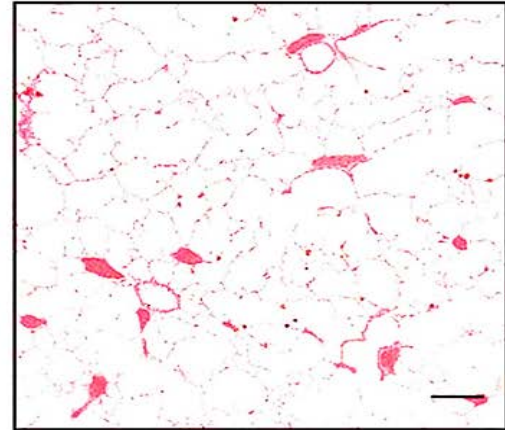
PBS



0 mg/ml Nicotine



18 mg/ml Nicotine





The Journal of Clinical Investigation

Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine

Matthew C. Madison, ... , David B. Corry, Farrah Kheradmand

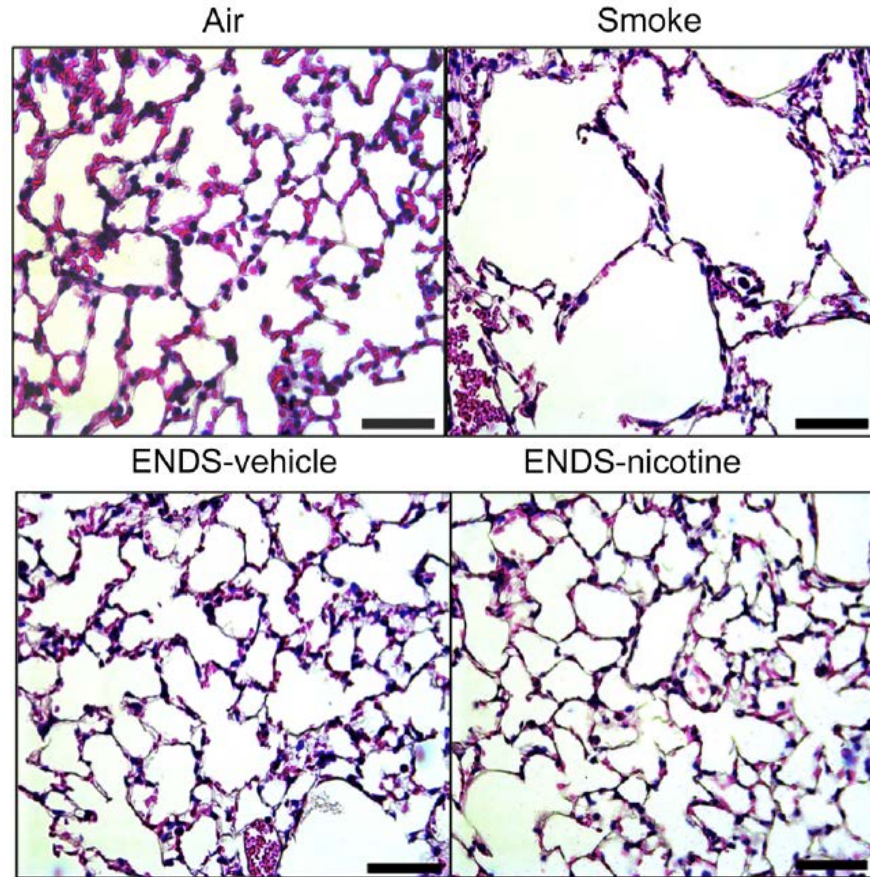
J Clin Invest. 2019. <https://doi.org/10.1172/JCI128531>.

Research Article

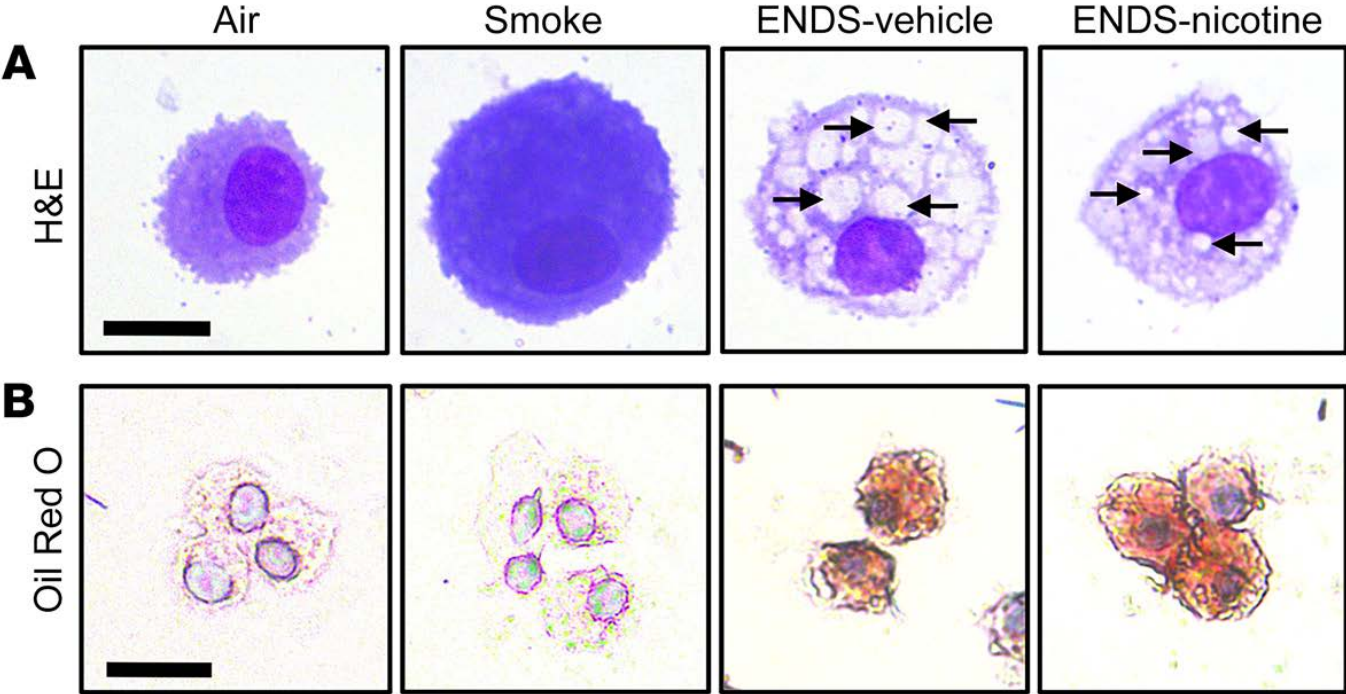
Immunology

Inflammation

Histological Changes in Lung Tissues Following 4 Months of Exposure



Lipid Accumulation in Alveolar Macrophages



Conclusions: Nicotine and Respiratory Disease

- Biological plausibility that nicotine may result in greater and/or more severe respiratory infection risk
- While such risk has been observed in cigarette smokers, there are no data in snus or e-cigarette users
- Conflicting evidence on nicotine and emphysematous changes



FDA STATEMENT

**Statement from FDA Commissioner Scott
Gottlieb, M.D., and Principal Deputy
Commissioner Amy Abernethy, M.D., Ph.D., on
FDA's ongoing scientific investigation of
potential safety issue related to seizures
reported following e-cigarette use,
particularly in youth and young adults**

For Immediate Release: April 03, 2019

Statement From: Commissioner of Food and Drugs - Food and Drug Administration
Scott Gottlieb M.D.
Principal Deputy Commissioner - Office of the Commissioner
Amy Abernethy MD PhD.

Conclusions

- Nicotine can potentially affect every organ system in the body. Various potential harmful effects and mechanisms are suggested by studies of nicotine in cells and animals.
- Addiction is expected with regular use of nicotine, but its health consequences are determined primarily by the delivery system
- Primary nicotine addiction associated with vaping in non-smokers (youth and young adults) is increasing with unknown long-term health consequences

Conclusions

- Nicotine is a reproductive hazard and should be avoided during pregnancy, unless it is used to support smoking cessation
- Nicotine is much less hazardous to cardiovascular health than smoking, but may contribute to acute CV events, particularly in the presence of CV disease
- There is biological plausibility for nicotine to enhance infectious disease risk, promote cancer and to contribute to chronic lung disease, but risk likely low based on safety record of Swedish snus

**SAFETY IS NOT AN
ABSOLUTE MEASURE BUT
RATHER REFLECTS A
CONCLUSION THAT THE
DRUG'S BENEFITS
OUTWEIGH THE RISKS**

Q&A

- Submit questions via the **chat box**



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1-800-QUIT-NOW
Call. It's free. It works.
1-800-784-8669
For details on your state services, go to: <http://map.naquitline.org>



- ✓ Refer your clients to cessation services

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Behavioral Health Accreditation

California Association of Marriage and Family Therapists (CAMFT)

This webinar is accredited through the CAMFT for up to **1.0 CEU** for the following eligible California providers:

- Licensed Marriage and Family Therapists (LMFTs)
- Licensed Clinical Social Workers (LCSWs)
- Licensed Professional Clinical Counselors (LPCCs)
- Licensed Educational Psychologists (LEPs)

California Behavioral Health & Wellness Initiative

For our CA residents, we are working in CA helping behavioral health organizations go tobacco free and integrating cessation services into existing services thanks to the support of the CTCP.

Free CME/CEUs will be available for all eligible California providers, who joined this live activity. You will receive a separate post-webinar email with instructions to claim credit.

Visit CABHWI.ucsf.edu for more information.

Post Webinar Information

- You will receive the webinar recording, presentation slides, information on certificates of attendance, and other resources, in our follow-up email. All of this information will be posted to our website.
- Instructions will be emailed after the webinar.

SCLC Recorded Webinar Promotion

SCLC is offering FREE CME/CEUs for our 2017 and now **2018** recorded webinar collections for a total of 22.5 units.

Visit SCLC's website at:

<https://smokingcessationleadership.ucsf.edu/webinar-promotion>
for more information.

Save the Date

SCLC's next live webinar

- **January 30, 2020**
- On the social stigma of smoking with Dr. Jason Satterfield of UCSF
- Registration will be available after the New Year!

Contact us for technical assistance

- Visit us online at smokingcessationleadership.ucsf.edu
- Call us toll-free at **877-509-3786**
- Please complete the post-webinar survey

UCSF Smoking Cessation
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