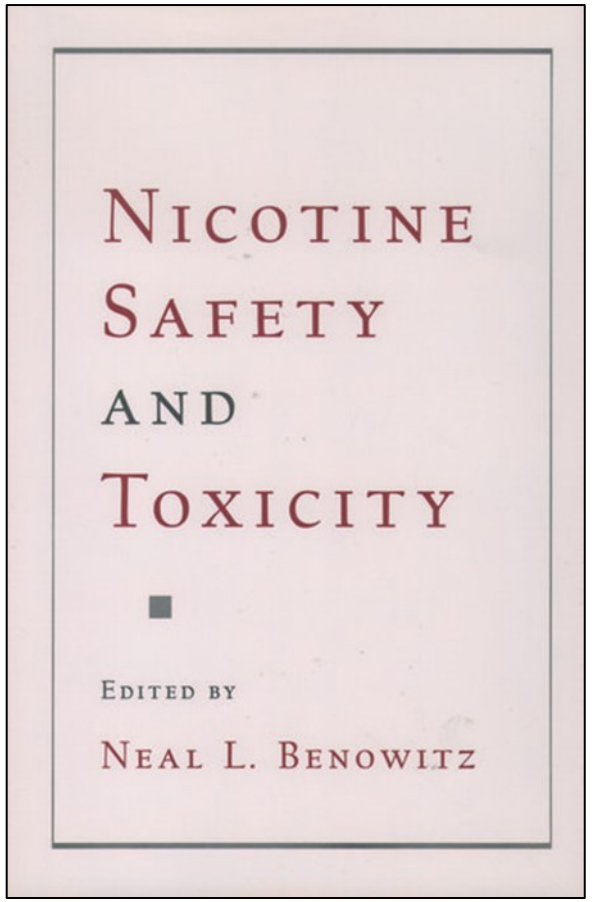
Risks and Benefits of Consumer Nicotine Delivery Systems

Welcome to the 2024, 27th Nicotine and Tobacco Conference

THEME THIS YEAR:

Risks and Benefits of Consumer Nicotine Delivery Systems: Emerging Evidence and Open Questions



August 1998

…and behind the curtain the real work gets done, so we need to thank…

- Avery Roberson
- Zack Olson
- Courtney Usher
- Michelle Forster
- Asia Abad

Adrian
5-days old
today

August 1998 rationale

- ***Nicotine as a replacement therapy:***
  - ***Smoking cessation***
  - ***Possibly for long-term maintenance of non-smoking***

- ***Potential vs. medical disorders:***
  - ***Ulcerative colitis, Alzheimer's disease, Parkinson's disease, Tourette's syndrome, attention deficit disorder, spasticity, and sleep apnea***

October 2024 rationale

- ***2009:** Congress integrates tobacco harm reduction into FDA umbrella (FDA-CTP)*
- ***2009-2024:** Wide array of consumer nicotine products developed*
- ***2024:** Tobacco harm reduction remains controversial*
  - *Risks and harms?*
  - *Benefits?*
  - *Short-term and long-term impacts?*
- ***NTSC 2024:** We hope to update the science on the risk and benefits of nicotine in different user groups including adults who smoke and non-smoking youth*

Moderator: Neal Benowitz
Session 2: Safety and Toxicity of Nicotine Delivery Devices

1. Neal Benowitz *UCSF*	**A) Nicotine Pharmacology and Safety Concerns** **B) Cardiovascular Toxicity of Nicotine: Implications for Harm Reduction**
2. Suchitra Krishnan-Sarin *Yale University*	**Youth Addiction and Mental Health**
3. Michael Ussher *University of London*	**Vaping During Pregnancy: A Systematic Review of Health Outcomes**
< Break >	

Session 2: Safety and Toxicity of Nicotine Delivery Devices

4. Steve Cook *University of Michigan*	**The Past is Prologue: Epidemiology of Exposure and Harm**
5. Cindy Chang *FDA-CTP*	**Biomarkers of Potential Harm by Tobacco Product Use**
6. Panel Discussion	**Kevin Gray** *MUSC* **Jed Rose** *Rose Research Center* **Ted Wagener** *Ohio State*

Day 2
Session 2: Safety and Toxicity of Nicotine Delivery Devices

Neal Benowitz
UCSF

A) Nicotine Pharmacology and Safety Concerns

B) Cardiovascular Toxicity of Nicotine: Implications for Harm Reduction

Nicotine Pharmacology and Safety Concerns

Neal L Benowitz MD
University of California
San Francisco

Nicotine and Tobacco
Science Conference
MUSC
Oct 29, 2024

UCSF Center for Tobacco Control Research and Education

Disclosures

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

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Pharmacology and toxicology of nicotine

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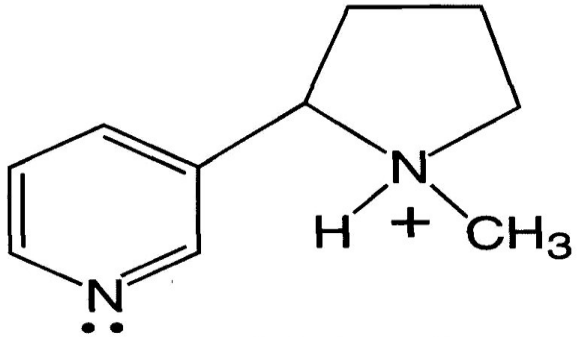
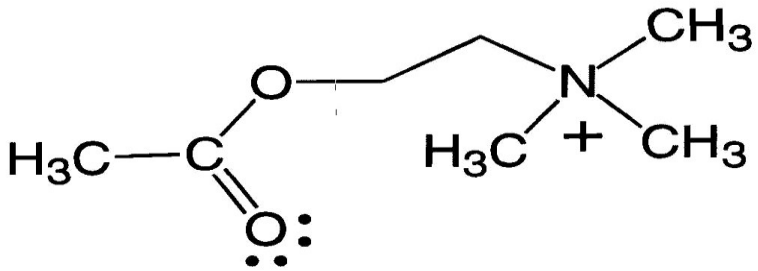
Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to "Nicotinic Cholinergic Receptors"



NICOTINE



ACETYLCHOLINE

Nicotine and discovery of receptor theory of drug action

ON THE REACTION OF CELLS AND OF NERVE-ENDINGS TO CERTAIN POISONS, CHIEFLY AS REGARDS THE REACTION OF STRIATED MUSCLE TO NICOTINE AND TO CURARI. By J. N. LANGLEY, *Professor of Physiology in the University of Cambridge.* (Eight Figures in the Text.)

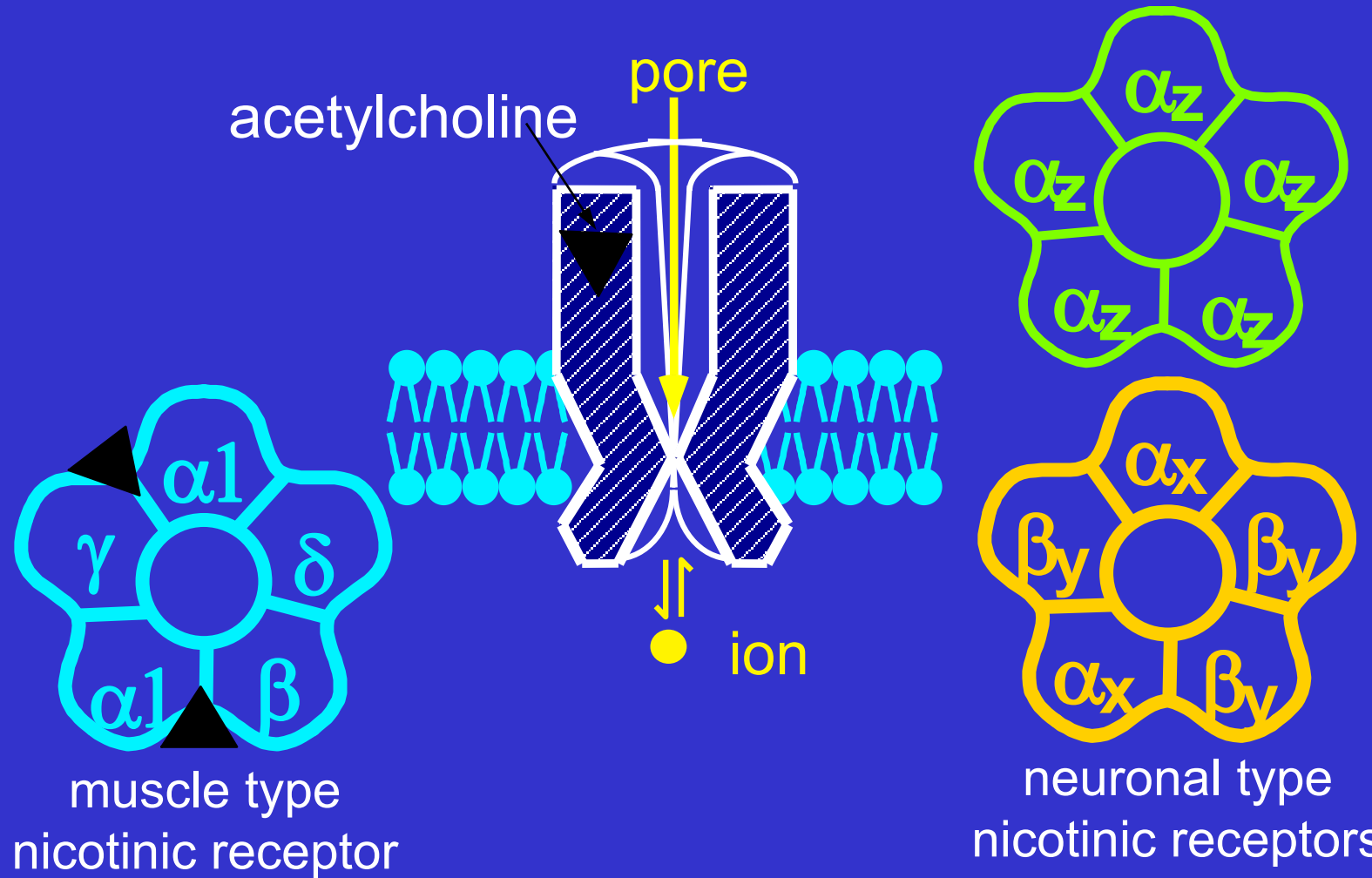
(*From the Physiological Laboratory, Cambridge.*)

CONTENTS

J Physiol 1905

- John Newport Langley, Cambridge physiologist
- Concept of "receptive substances" (cell receptors) based on studies of nicotine and curare
- Nicotine contraction of muscle in fowl even after denervation, abolished by curare, brought on again by higher doses of nicotine

Structure of Nicotinic ACh Receptors



Picciotto M. Emerging neuronal nicotinic receptor targets. SRNT 9th Annual Meeting; February 2003; New Orleans, La.

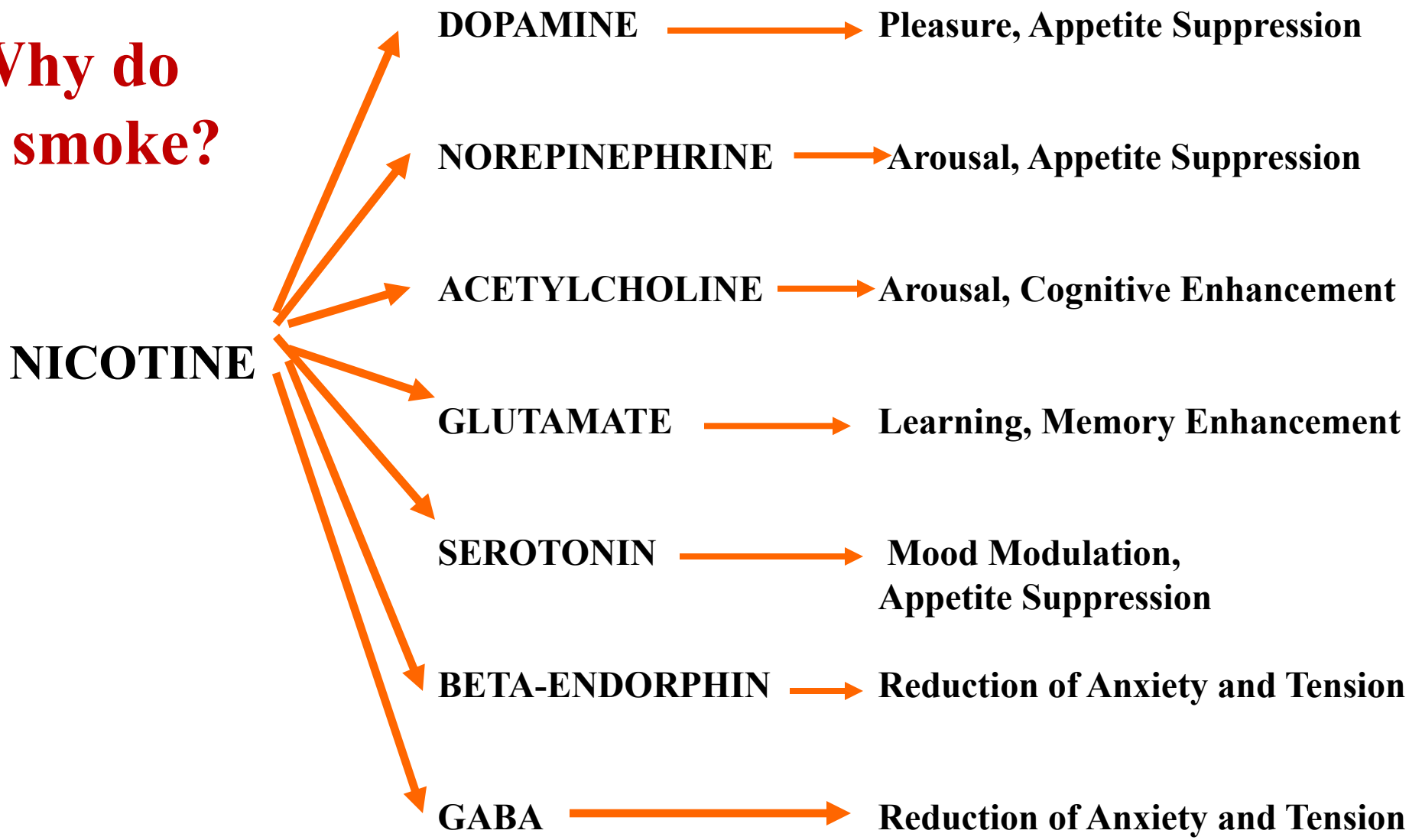
Receptor actions by which nicotine might cause harm

NAChR subtype	Effects
• α4β2*	• Dopamine release, addiction, neuroplasticity
• α3β4	• Sympathetic stimulation, catecholamine release, CV toxicity
• α7 homomeric	• Endothelial dysfunction, enhanced angiogenesis, inhibition of apoptosis, anti-inflammation

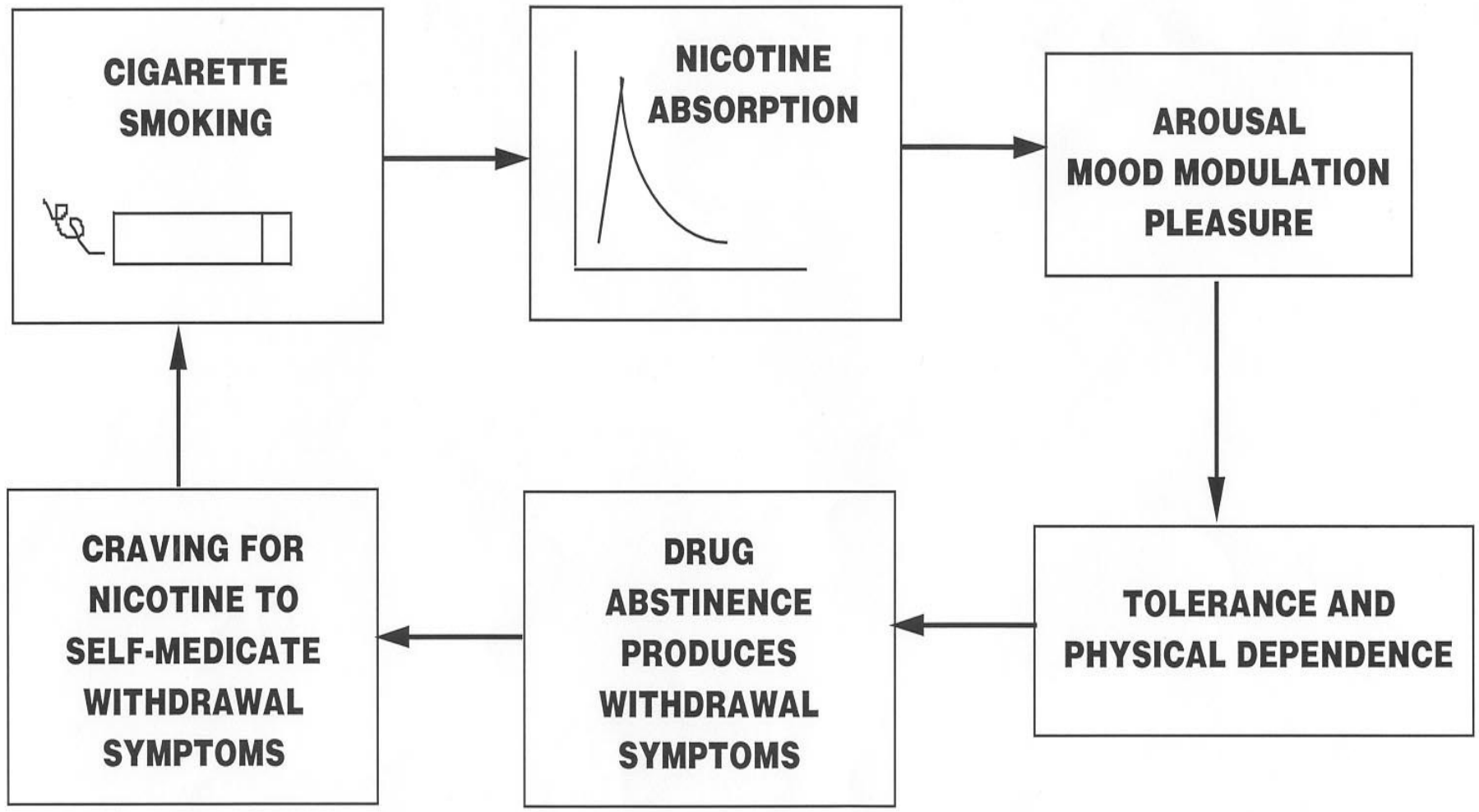
Caveat regarding in vitro studies-normal homeostatic mechanisms not operative

Nicotine Addiction

Why do people smoke?



NICOTINE ADDICTION CYCLE



Benefits of nicotine use

Medical

- Nicotine replacement medication
- ? Ulcerative colitis
- ? ADHD
- ? Parkinson's disease
- ? Autoimmune diseases

Caveat: some perceived beneficial effects related to reversal of withdrawal symptoms

Non-medical

- Pleasure
- Stimulation
- Cognitive enhancement
- Relaxation
- Mood modulation
- Psychiatric benefit
- Enhanced athletic performance
- Weight control

Major Safety Concerns for Nicotine

• Addiction	• Definite
• Cardiovascular disease	• Probable
• Reproductive Toxicity	• Probable
• Impaired Adolescent Brain development	• Possible
• Infectious Disease Risk	• Possible
• Cancer	• Possible
• Chronic lung disease	• Unlikely

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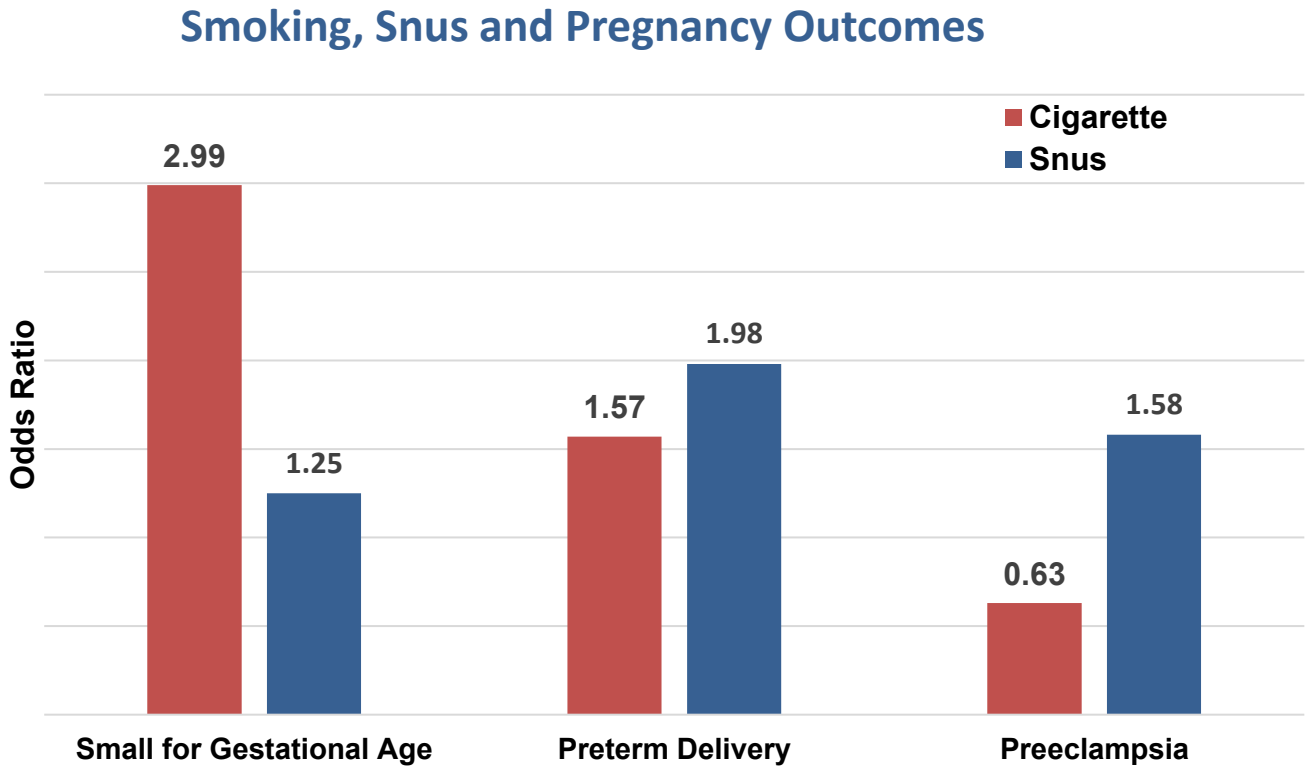
Reproductive Toxicity

Reproductive Toxicity of Nicotine

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



England, Am J Obgyn, 2003

Infectious Disease Risk

Nicotine and Infectious Disease Risk

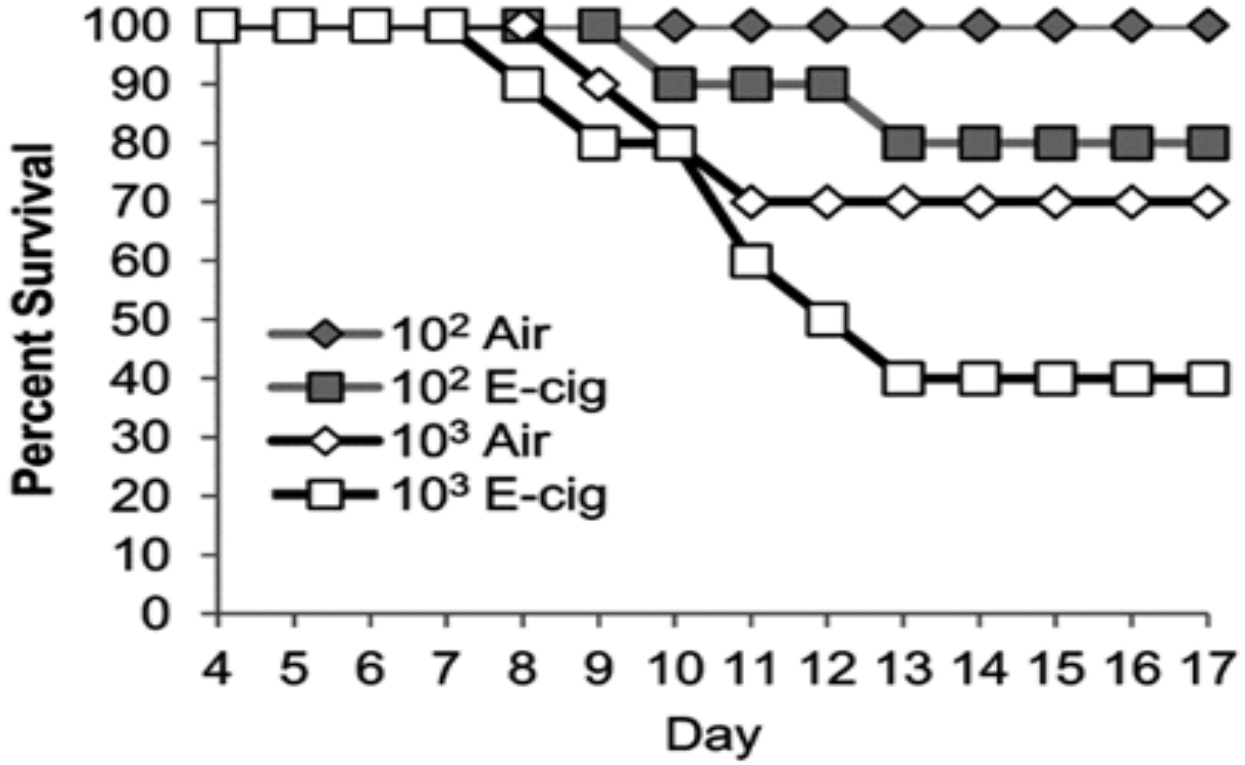
Nicotine cholinergic immunosuppression:

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



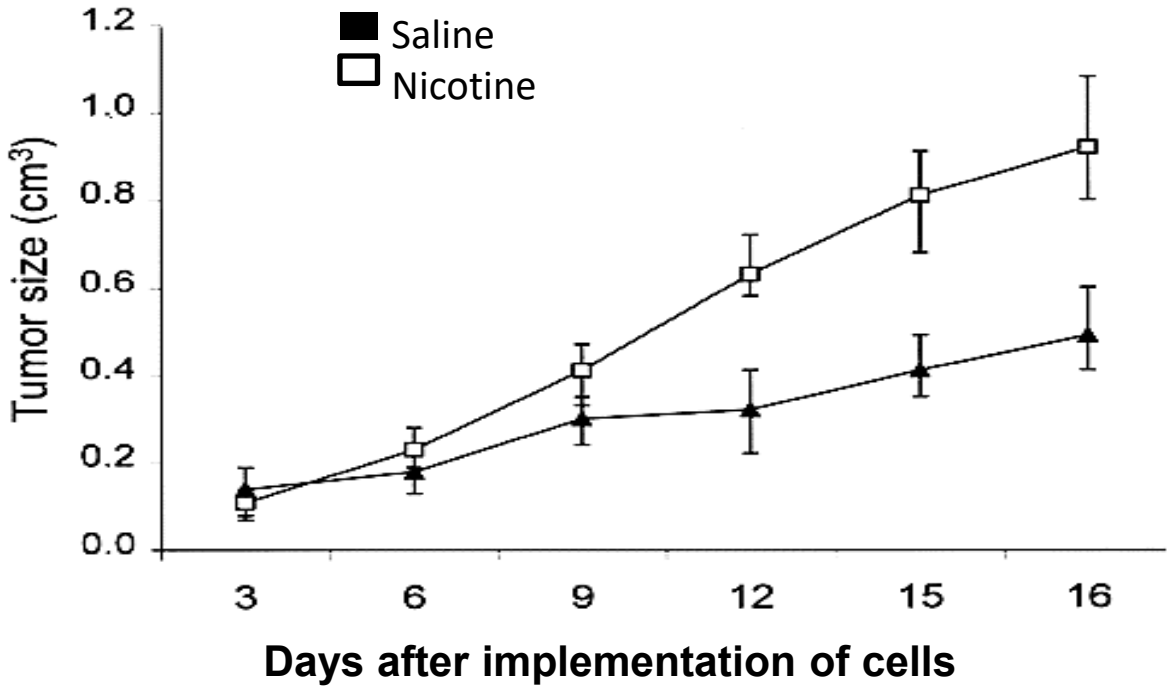
Sussan, PLoS ONE 2015

Cancer Risk

Nicotine and Cancer

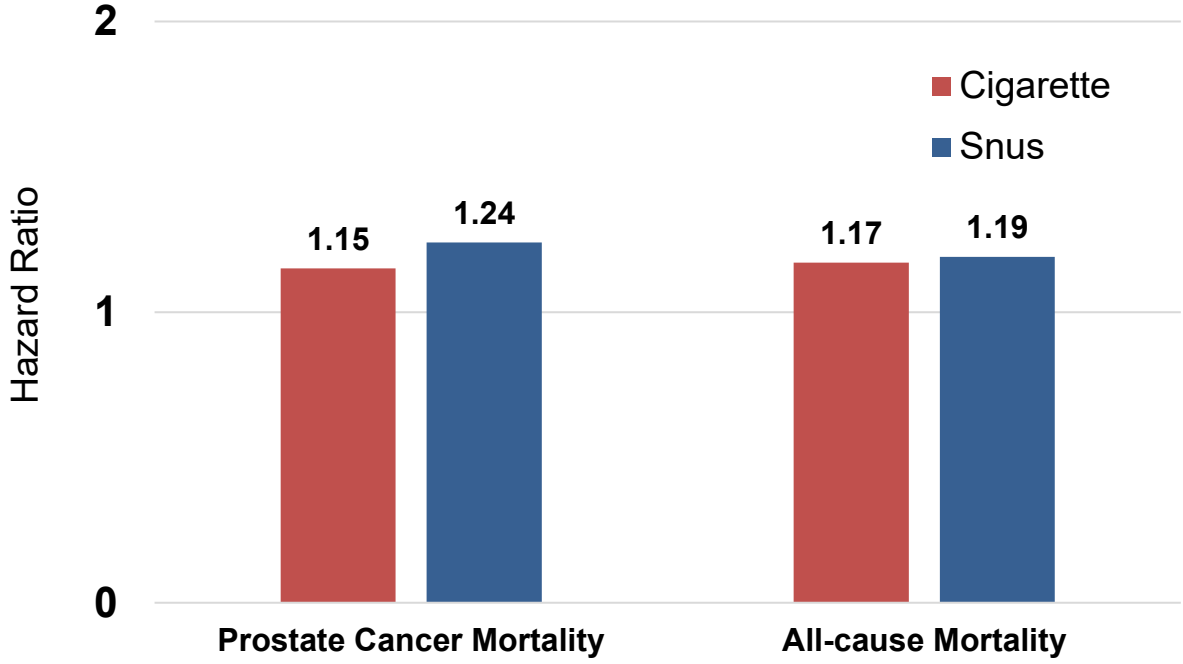
- Nicotinic receptors on many cells, including cancer cells
- Enhancement of cell growth (cell proliferation and migration; angiogenesis)
- Stimulation of cell survival (inhibition of apoptosis)
- Animal studies: enhanced tumor growth and metastasis; resistance to cancer chemotherapy drugs
- Human snus epidemiology
  - No evidence of cancer causation except pancreatic and esophageal, nitrosamine-related
  - Increased prostate cancer mortality

Tumor Growth in the Lewis Lung Cancer Cells



Heeschen, Nature Medicine, 2001

Tobacco Use and Prostate Cancer Survival



Wilson, Int J Ca, 2016

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. Its health consequences are determined primarily by the delivery system, but addiction per se may be harmful to some.**
- **Nicotine can impair adolescent brain development in animals, but effects in adolescent nicotine users still uncertain.**

Conclusions

- Nicotine is a reproductive hazard and its use during pregnancy is of concern. Benefits of non-combusted nicotine to aid smoking cessation may outweigh risks.
- 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.
- Except for Swedish snus, there are relatively few studies of long term non-combusted nicotine use in humans. Long-term studies of the safety of ENDS and newer oral nicotine products with appropriate control for prior combusted tobacco use history, temporality and dose-response are needed.

Cardiovascular Toxicity of Nicotine: Implications for Tobacco Harm Reduction

Neal L Benowitz MD

Professor Emeritus of Medicine
University of California San Francisco

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Cardiovascular Disease Caused by Cigarette Smoking

Acute Vascular Events

- **Acute myocardial infarction**
- **Sudden death**
- **Stroke**
- **Restenosis after coronary bypass, angioplasty, thrombolysis**

Accelerated Atherosclerosis

- **Coronary arteries**
- **Peripheral arteries**
- **Carotid, cerebrovascular arteries**
- **Aortic aneurysm**

Other

- **Aggravation of heart failure**
- **Atrial fibrillation**
- **Impaired wound healing**

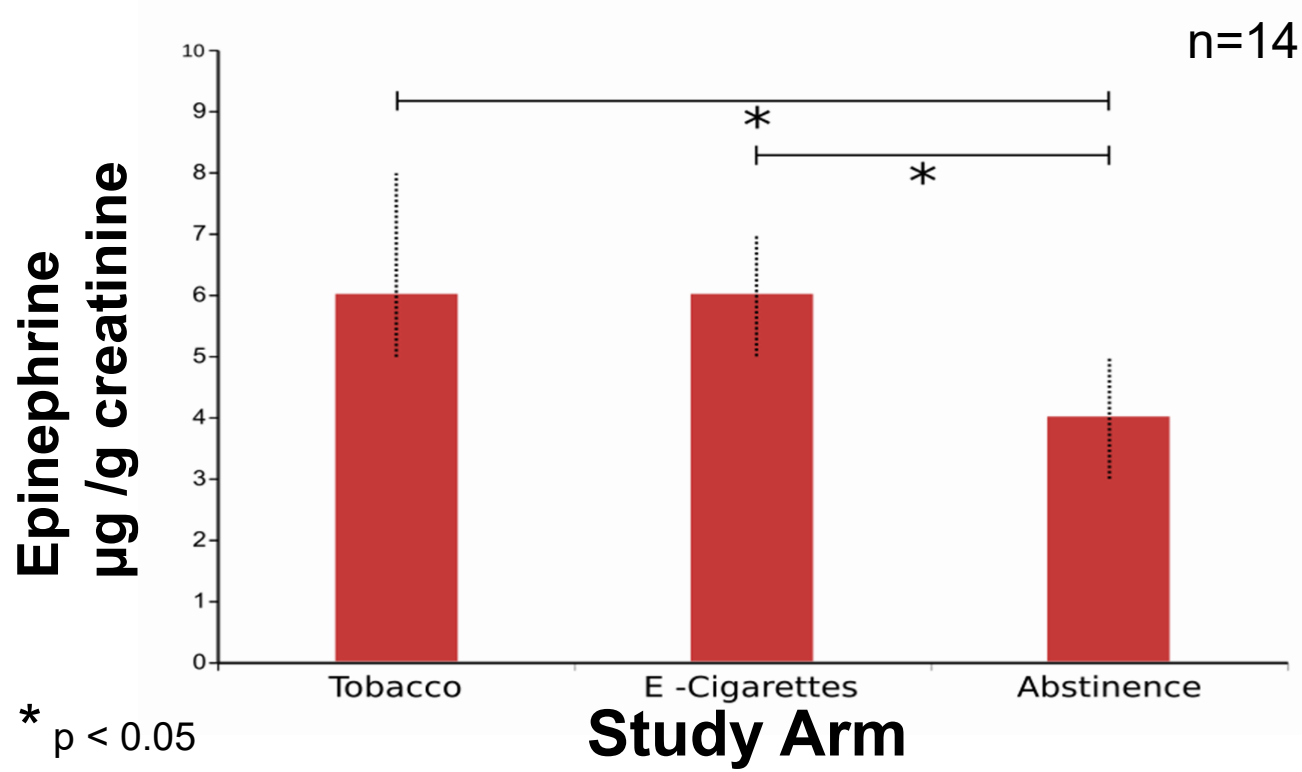
Mechanisms and potential cardiovascular harms of nicotine

- Hemodynamic effects
- Arrhythmogenesis
- Endothelial dysfunction
- Angiogenesis
- Myocardial remodeling
- Lipid abnormalities
- Insulin resistance
- Inflammation

- Definite
- Probable
- Possible
- Possible
- Possible
- Possible
- Possible
- Unlikely

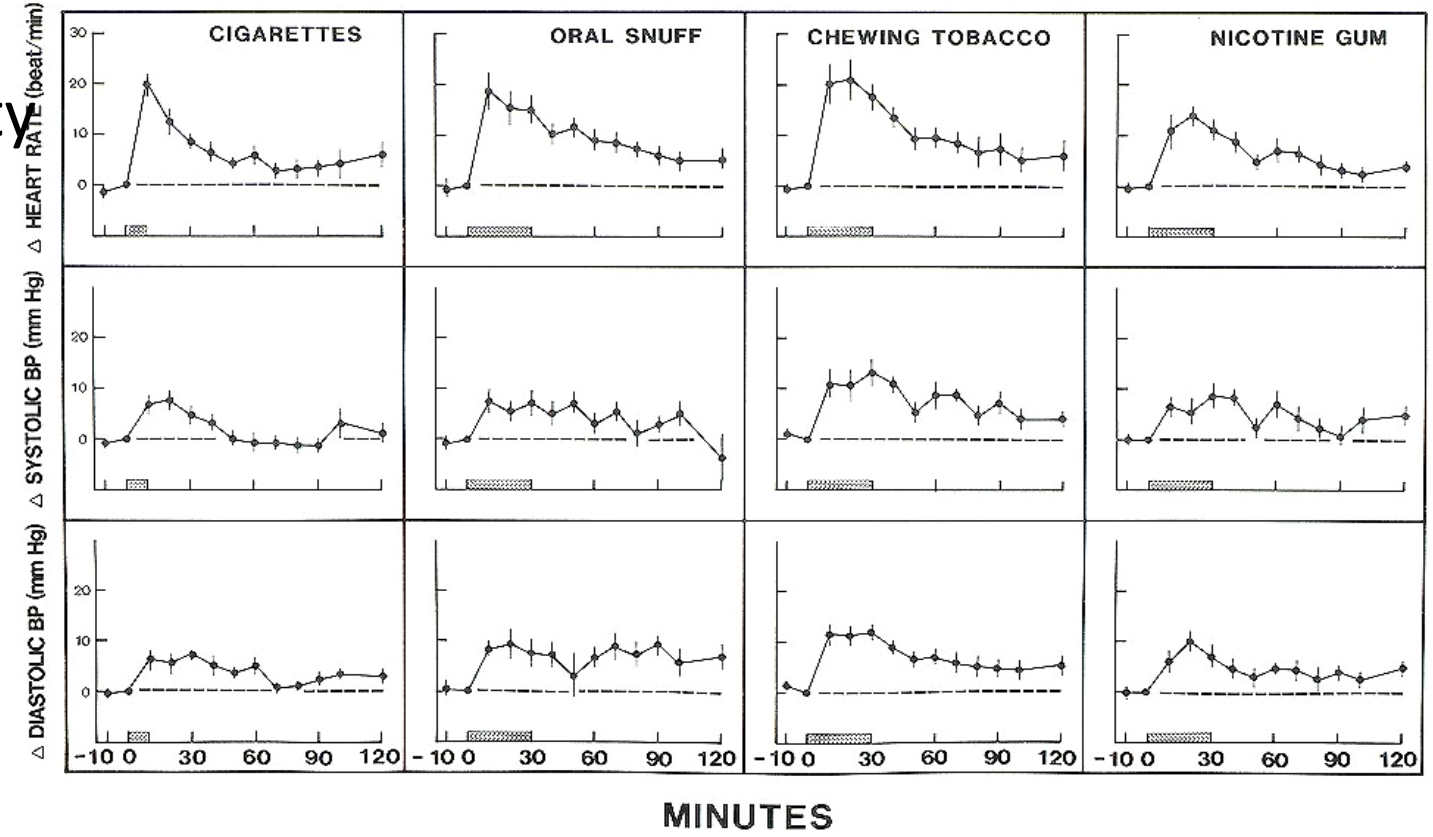
Consequences of Nicotine-induced Sympathetic Neural Stimulation

- Hemodynamic (increased BP, HR, cardiac contraction, constriction of blood vessels)
- Arrhythmogenesis
- Lipid abnormalities
- Insulin resistance & Diabetes
- Inflammation



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



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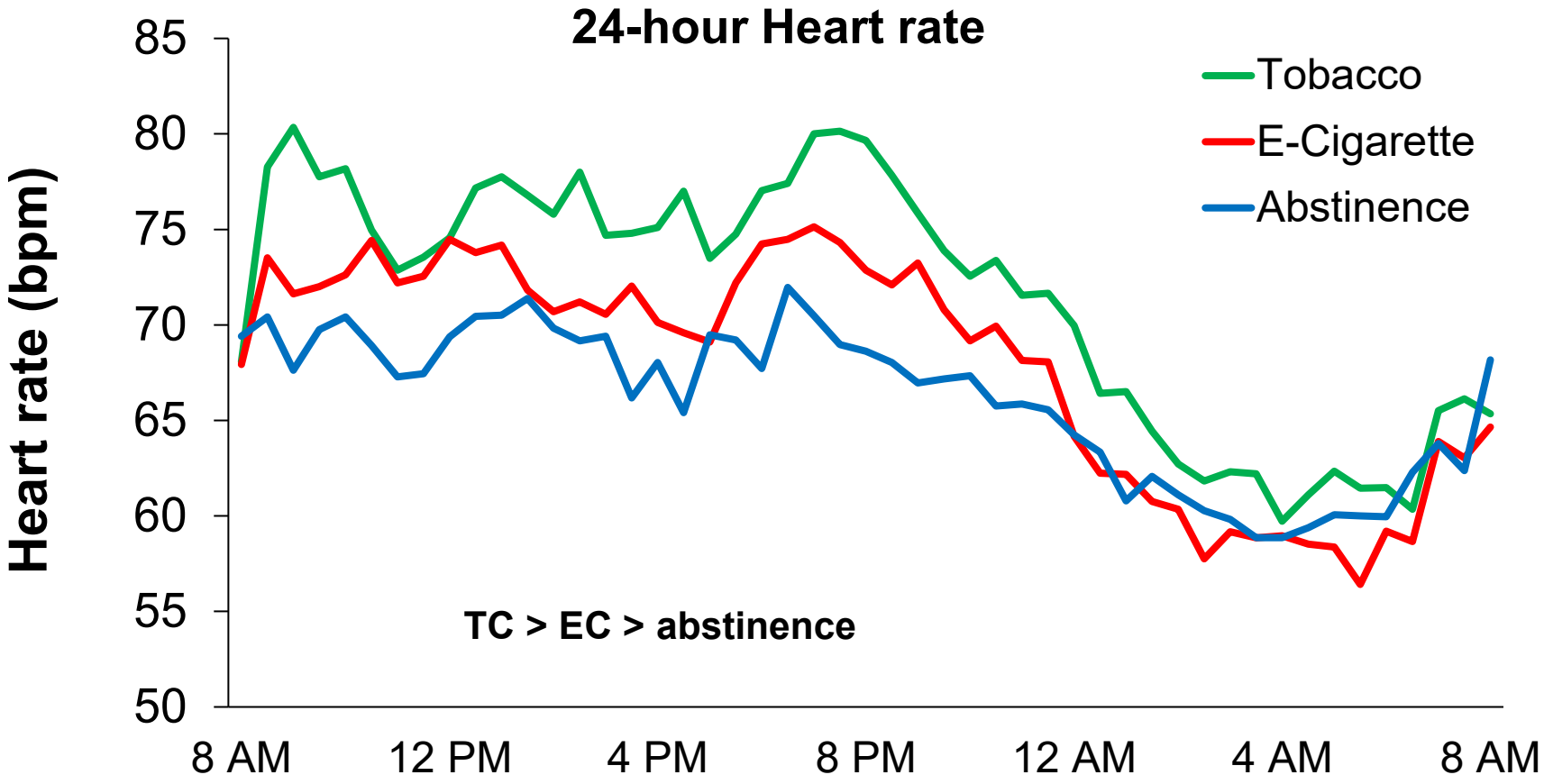
Daily smoking, e-cigarette use and heart rate acceleration



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Cardiovascular Effects of NRT and Smokeless Tobacco:

Natural Experiment on Effects of Nicotine without Combustion Toxicants

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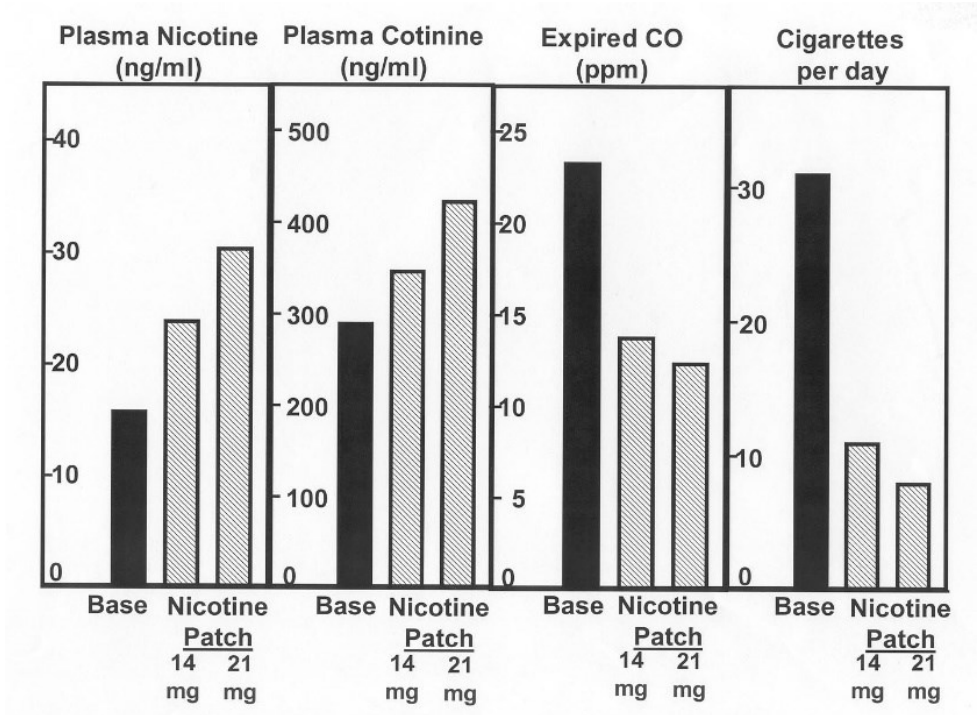
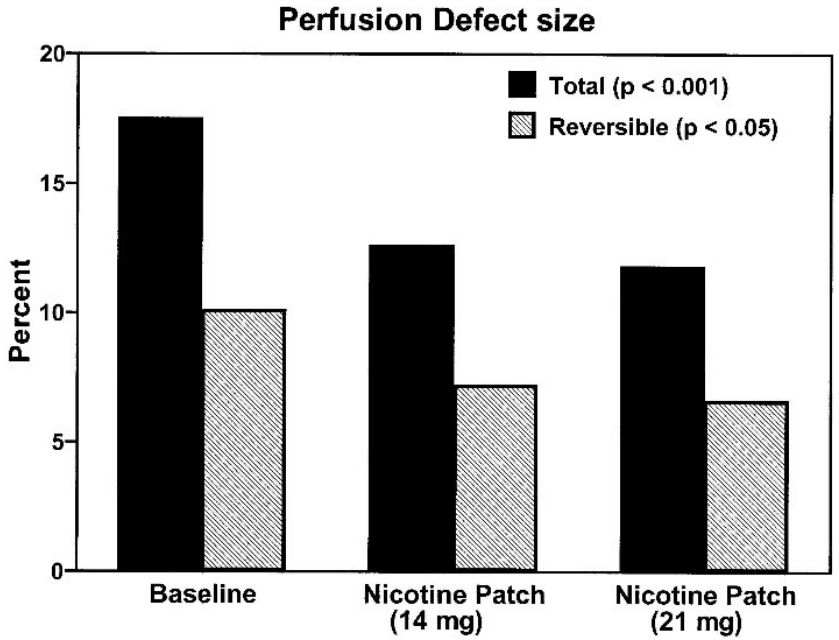
Nicotine Medication and Cardiovascular Disease

Transdermal Nicotine Increases Nicotine Levels but Suppresses Smoking: Myocardial Perfusion Improves





(Mahmarian, 1997)

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Nicotine-Replacement Studies Conducted in Patients With Cardiovascular Disease

Study	N	Duration (Wks)	NRT	Serious Adverse Events*		Smoking Cessation	
				Active Treatment	Control	Active Treatment	Control
Working Group, 1994	156	5	Patch	3	8	36%	22%
Joseph, 1996	584	48	Patch	16	23	10%	12%
Tzivoni, 1998	106	2	Patch	2	1	27%	13%
Campbell, 1996	234	52	Patch	0	0	21%	14%
Kimmel, 2001	653 cases 2,990 controls		Patch	Odds ratio myocardial infarction = 0.46 (95% CI: 0.06, 1.47)		N/A	

*All serious adverse events reported in these studies were cardiovascular in nature with the exception of the Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease Study.[7] In this study 2 of 3 events in the active treatment group and 5 of 8 events in the control group were cardiovascular in nature.

Smokeless Tobacco and Cardiovascular Disease

Snus Products

Swedish snus

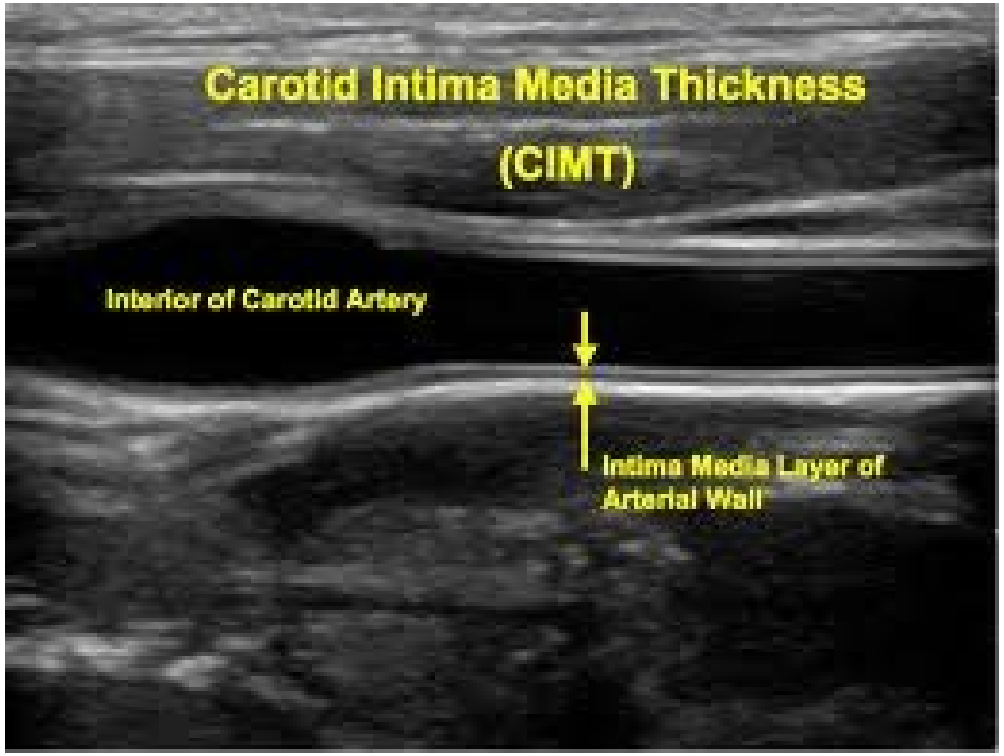
American snus

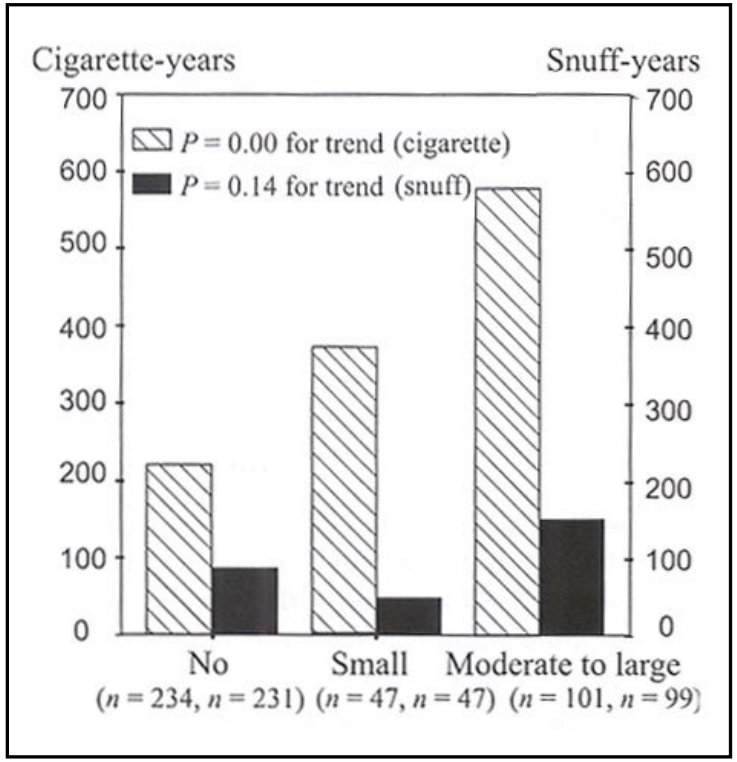
www.trinketsandtrash.org

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
- Conflicting data on increased risk of heart failure, lipid abnormalities, diabetes
- No biomarkers of CV harm in exclusive ST users (PATH)

Smokeless Tobacco Associated with Minimal Cardiovascular Risk





(Wallenfeldt, 2001)

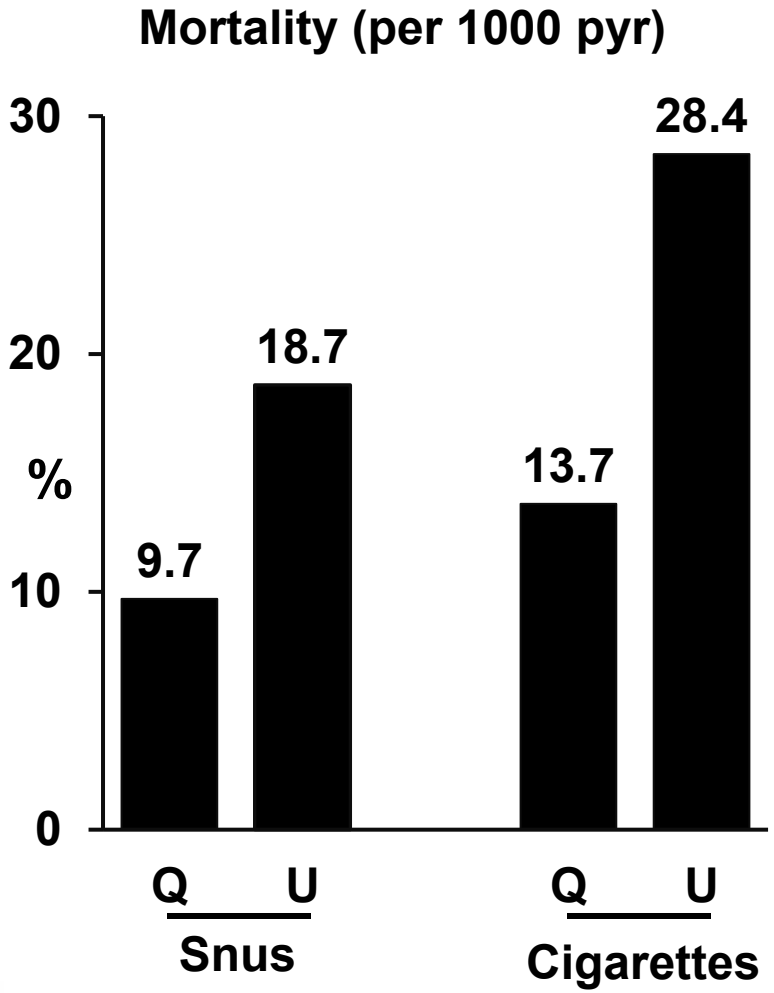
Continued Snus Use After Myocardial Infarction Increases Mortality

SWEDEHEART MI register

2474 snus users - 27% Quit

6934 smokers – 61 % Quit

2 year follow up



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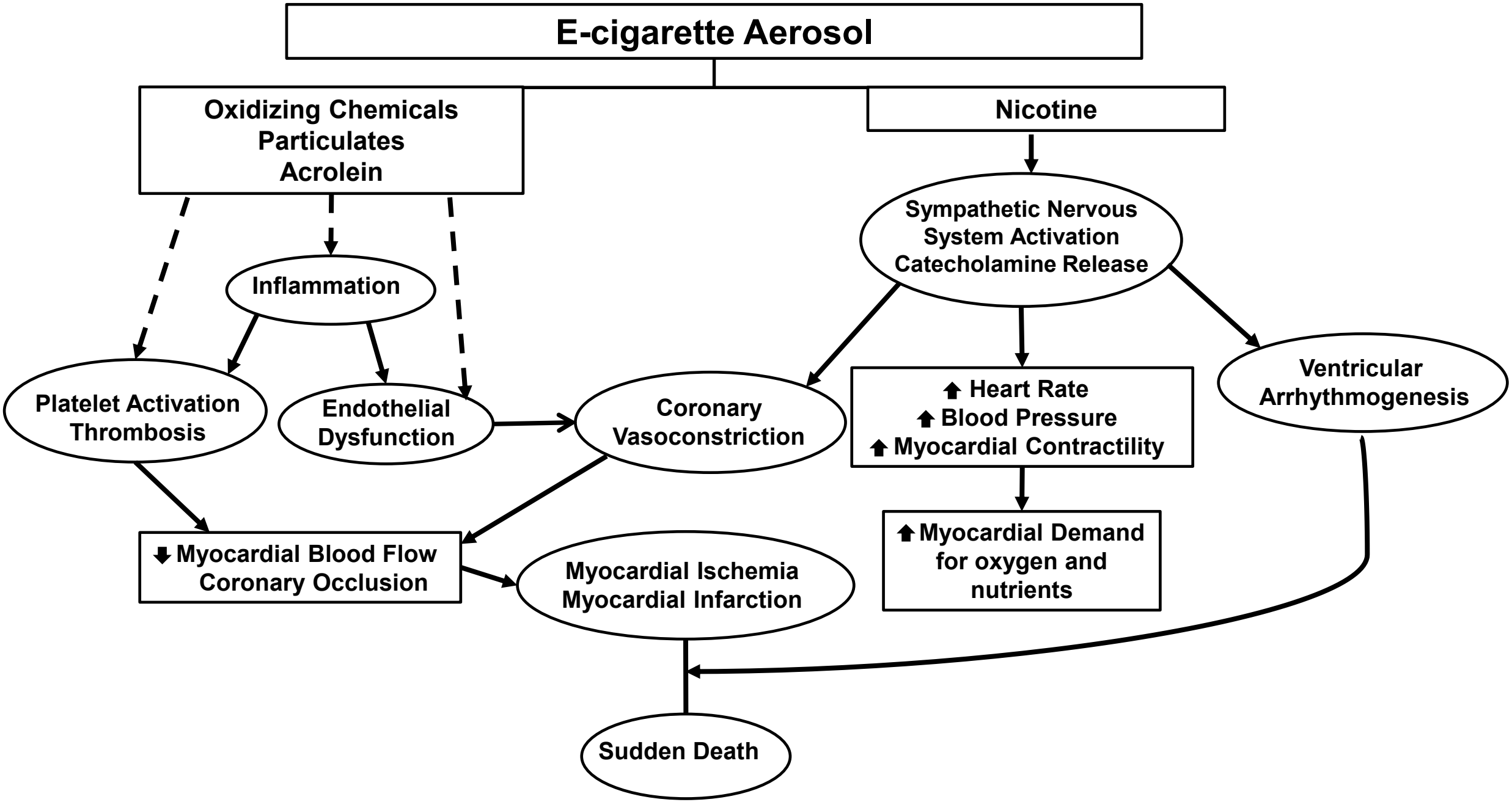
(Arefalk, 2014)

E-cigarettes and Cardiovascular Disease

Mechanisms by which E-cigarettes could cause Acute CV Events



Empirical Evidence on CV Effects of E-cigarettes in People

- Increased heart rate and blood pressure (nicotine effects). Reported association between EC use and high blood pressure
- Increased arterial stiffness (conflicting reports)
- Endothelial dysfunction (reduced FMD; increased circulating EPCs). Dysfunction appears to resolve with long term switching from smoking to vaping
- Oxidative stress (incr LDL oxidizability)
- Platelet activation
- Case reports of atrial fibrillation
- No reliable epidemiology for adverse CV events

NEJM Evidence

Published February 27, 2024
NEJM Evid 2024; 3 (3)
DOI: 10.1056/EVIDoa2300229

ORIGINAL ARTICLE

Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes

Stanton A. Glantz, Ph.D.,[1] Nhung Nguyen, Ph.D.,[2] and Andre Luiz Oliveira da Silva, Ph.D.[2]

"Pooled OR similar for EC and Cig for CVD, stroke and metabolic dysfunction.
Pooled OR greater for dual use v Cig for all outcomes"

Claims That E-Cigarettes Are as Bad as Cigarettes Are Premature and Misrepresent the Evidence

K. Michael Cummings, Ph.D., M.P.H.,[1] Nancy A. Rigotti, M.D.,[2] Neal L. Benowitz, M.D.,[3] and Dorothy K. Hatsukami, Ph.D.[4]

- Cross sectional studies – concluding causation problematic
- Smoking-related disease usually takes many year to develop. The same is likely true for E-cig-related disease
- Weak assessments of exposures and clinical outcomes
- No assessment of cigarette and E-Cig dose-response

- Most E-cig users are current or former smokers. Failure to assess temporal aspects of smoking and vaping in relation to disease onset
- Smokers may switch to vaping to reduce health risks after early symptoms develop
- No comparison of former smokers who vape with former smokers who quit without E-cig use
- No consideration of biological plausibility related to biomarker studies

Conclusions relating Nicotine and Cardiovascular Disease

- Biological plausibility and epidemiological evidence (snus) suggest that nicotine may contribute to acute CV events
- Short term nicotine use poses little CV risk
- Long term use may be harmful, especially in in the presence of CVD. We do not know for sure
- Risk undoubtedly much lower than cigarette smoking