

Electronic Cigarettes, Nicotine and Policy Implications

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Disclosures

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

My Big Picture Questions

- What are the harms of long-term use of nicotine delivered without tobacco combustion (e-cigarettes or other ANDS)?
- How best to regulate nicotine to eliminate cigarette smoking?

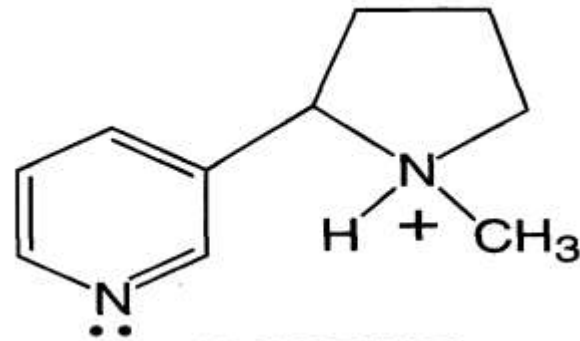
Outline

- Major nicotine safety concerns
- ECs and nicotine addiction in youth
- Daily nicotine exposure with various patterns of EC use
- Harms of nicotine – implications for long term use
- ECs, reduced nicotine content cigarettes and the cigarette end game

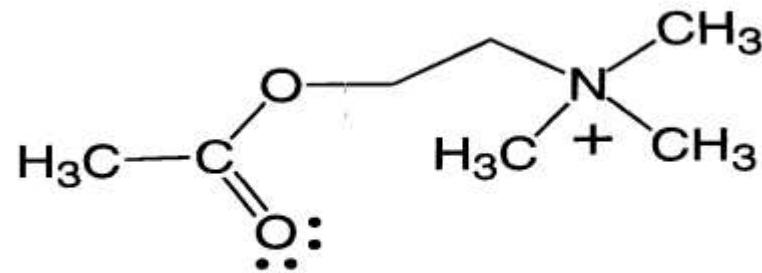
Nicotine Mimics the Neurotransmitter

Acetylcholine:

Both Bind to “Nicotinic Cholinergic Receptors”



NICOTINE



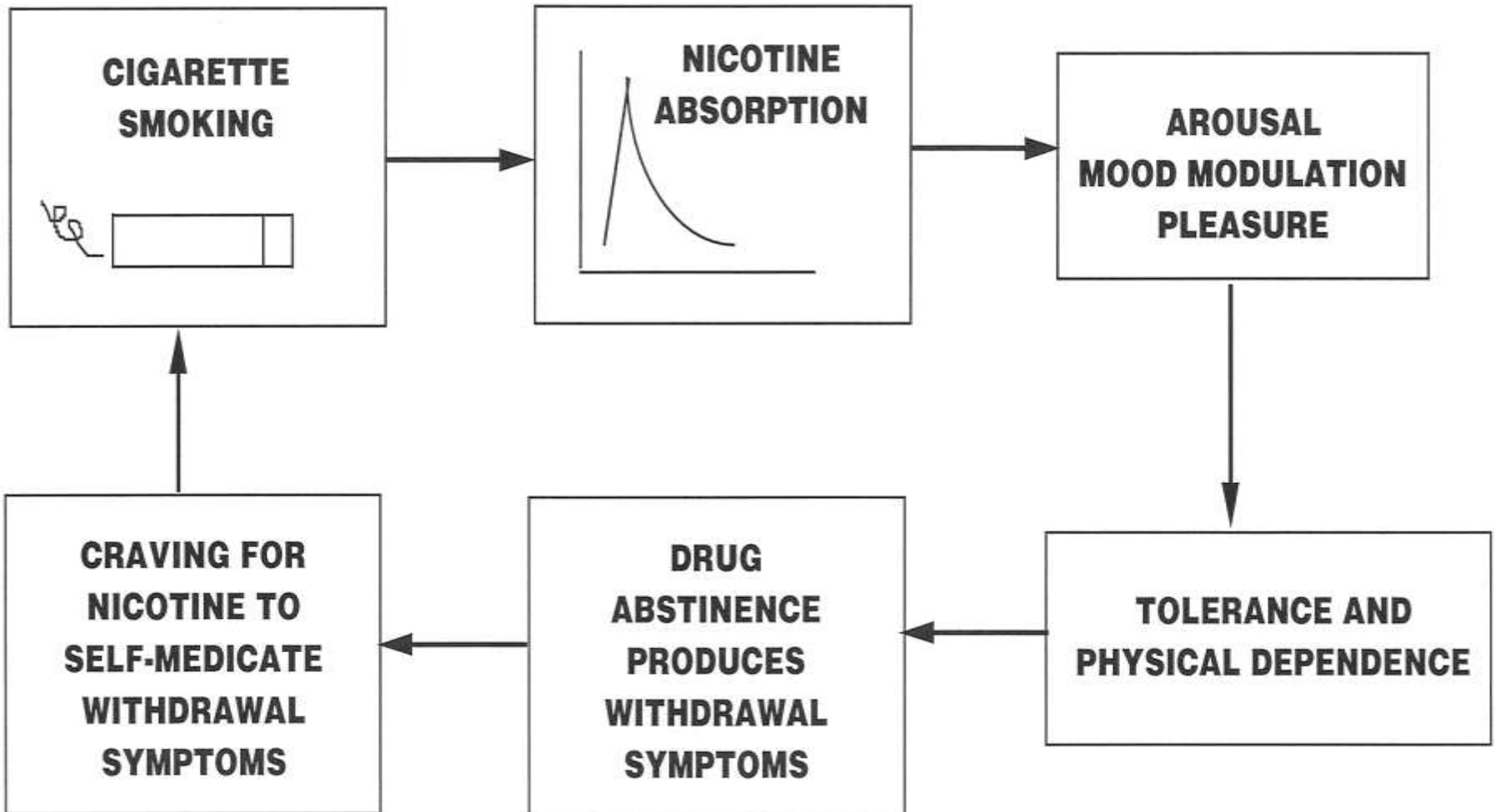
ACETYLCHOLINE

Major Safety Concerns for Nicotine

- **Addiction**
- **Cardiovascular Disease**
- **Reproductive Toxicity**
- **Infectious disease risk**
- **Cancer**
- **Definite**
- **Probable**
- **Probable**
- **Possible**
- **Unlikely**

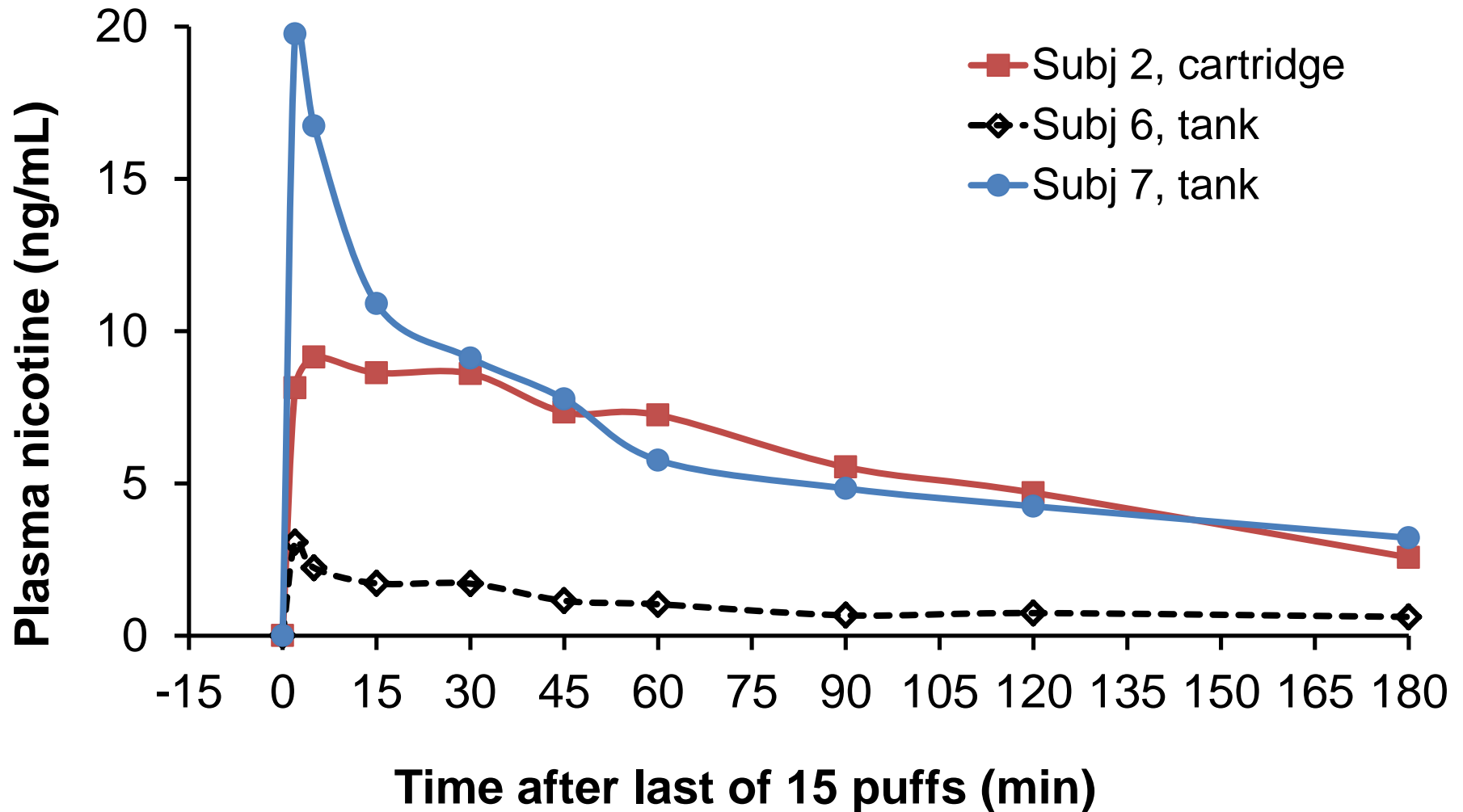
**E-cigarettes and Nicotine
Addiction:
Implications for EC use by
Youth**

NICOTINE ADDICTION CYCLE

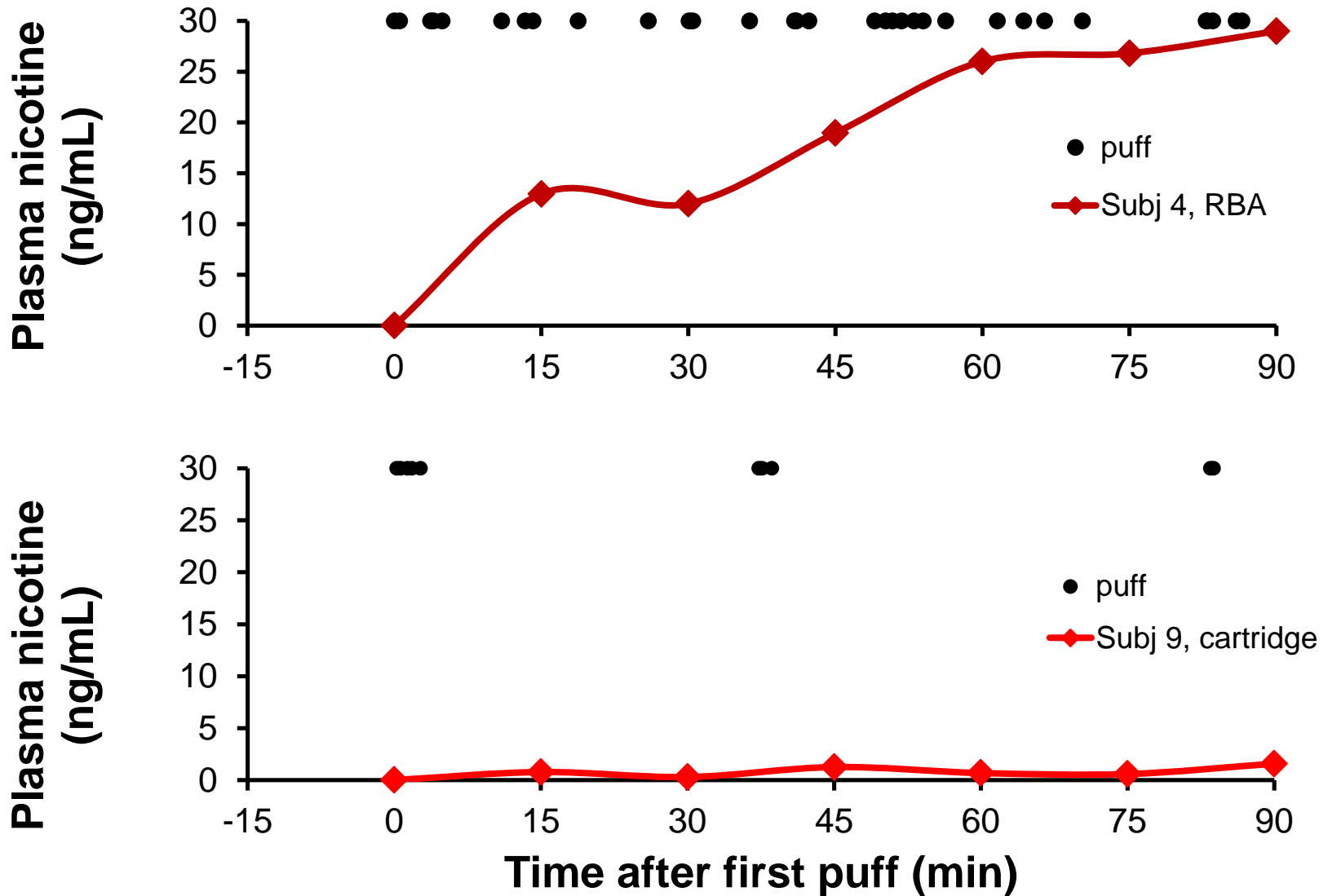


**Nicotine pharmacokinetic
profile differs by delivery
system –
could have implications for
addiction and other toxicity**

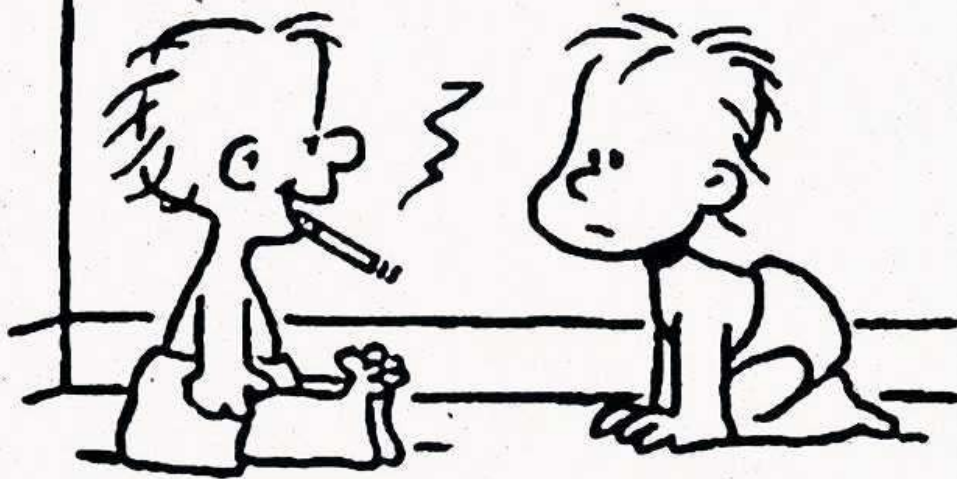
Nicotine PK with E-cigarette use during standardized session



Nicotine PK with ad libitum E-cigarette use



Berry's World



Jim Berry

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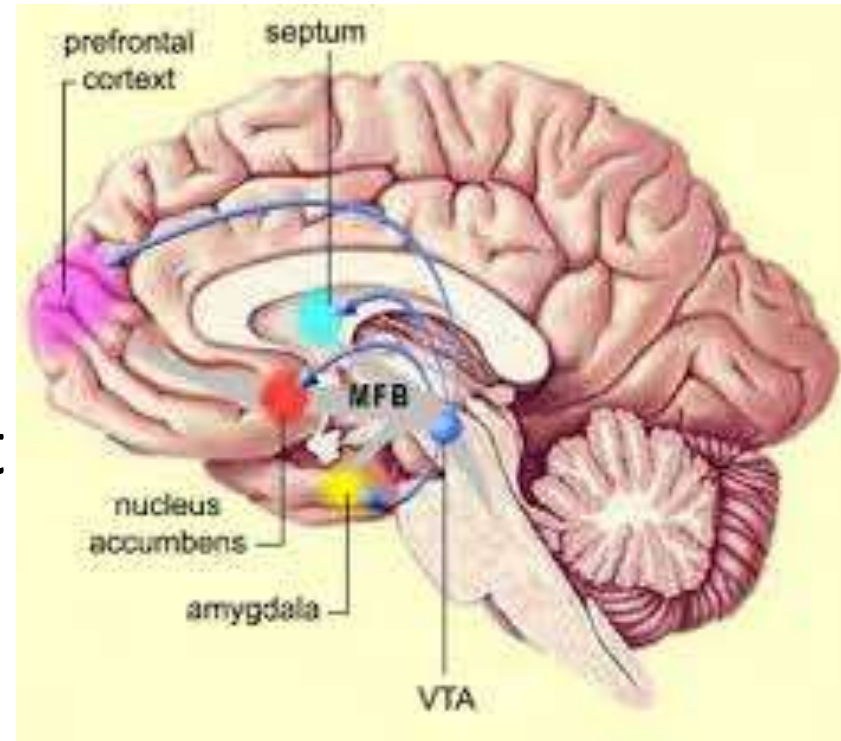
"Don't worry! I can quit any time I want."

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 effects on prefrontal cortex (PFC) functions

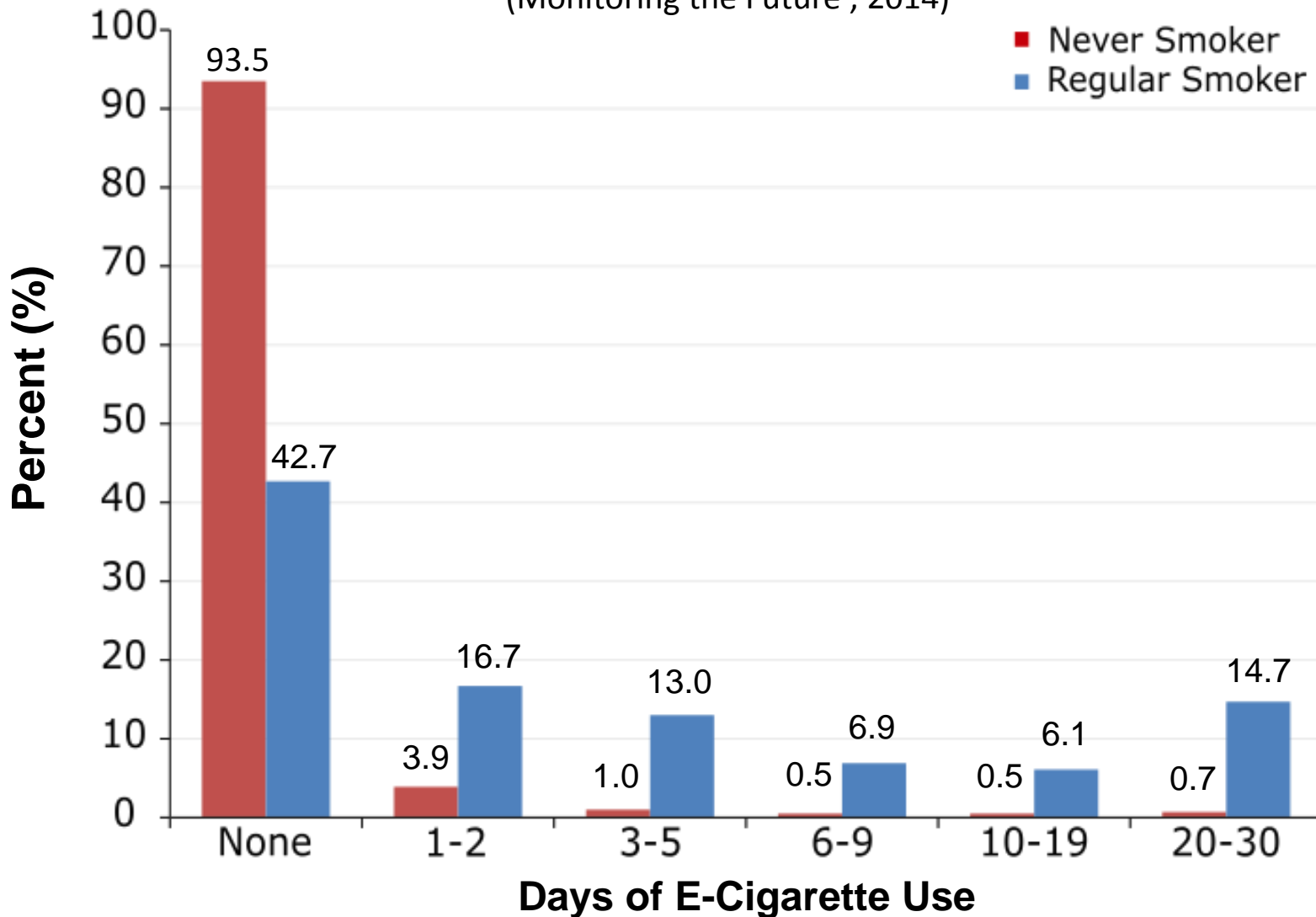
- Nicotine in adolescent rats results in long-term cognitive impairment (accuracy, impulse control)
- Adolescent smokers show reduced PFC activity, including memory and attention
- Adolescent smoking associated with later life behavior disturbances, including substance abuse and mental health problems
- Early initiation of smoking associated with higher level of addiction in adulthood

Addiction risk is likely less for EC compared to conventional cigarettes

- PK profile different – lower peak nicotine levels with usual patterns of use
- Cigarette smoke is more than nicotine – MAOI inhibition augments nicotine brain effects
- Youth epidemiology finds much experimentation, occasional use, use of non-nicotine containing liquids.
- Most likely most youth progression from EC to regular use or cigarette smoking is NOT mediated by nicotine addiction.

Number of Days of 12th Grade E-cigarette Use by Smoking Status, Last 30 Days

(Monitoring the Future, 2014)



(Warner, Am J Prev Med 2016)

Daily nicotine exposure with various patterns of EC use

- In former smokers, sole EC user have similar cotinine levels to typical cigarette smokers
- Experimental switching studies – EC users can achieve similar nicotine intake to when smoking
- In the general population most dual users are non-daily EC users – nicotine intake similar to smokers
- Dual users who use EC daily (and generally more advanced devices) report fewer CPD – I could not locate studies on nicotine intake

**Cardiovascular Toxicity of
Cigarette Smoking and E-
cigarettes:
What Role 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

CV Actions of Nicotine and Probable Contribution to Smoking-induced CVD

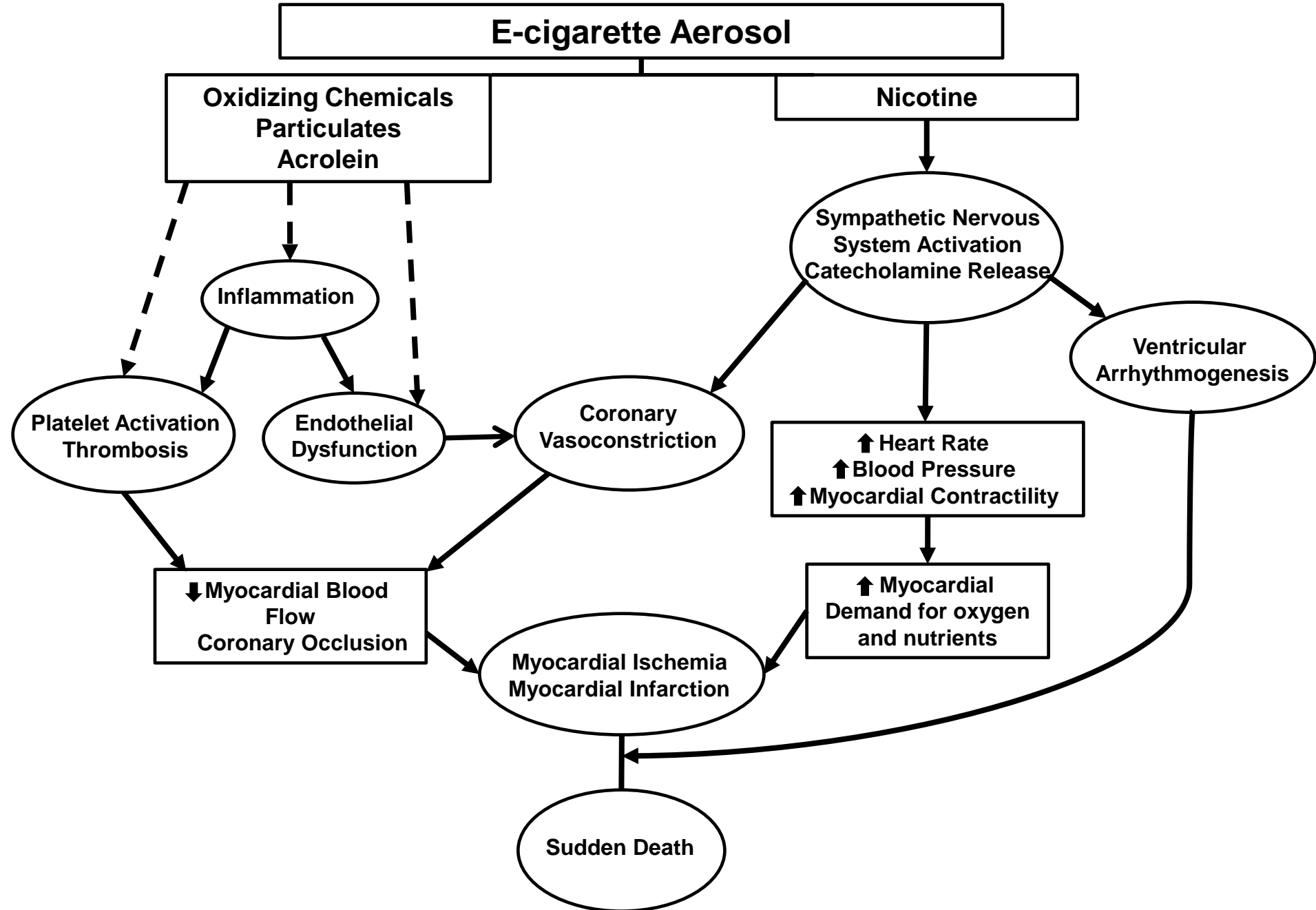
Action

- **Hemodynamic**
- **Endothelial Dysfunction**
- **Thrombogenesis**
- **Inflammation**
- **Arrhythmogenesis**
- **Lipid Abnormalities**
- **Insulin Resistance/Diabetes**
- **Myocardial Effects**

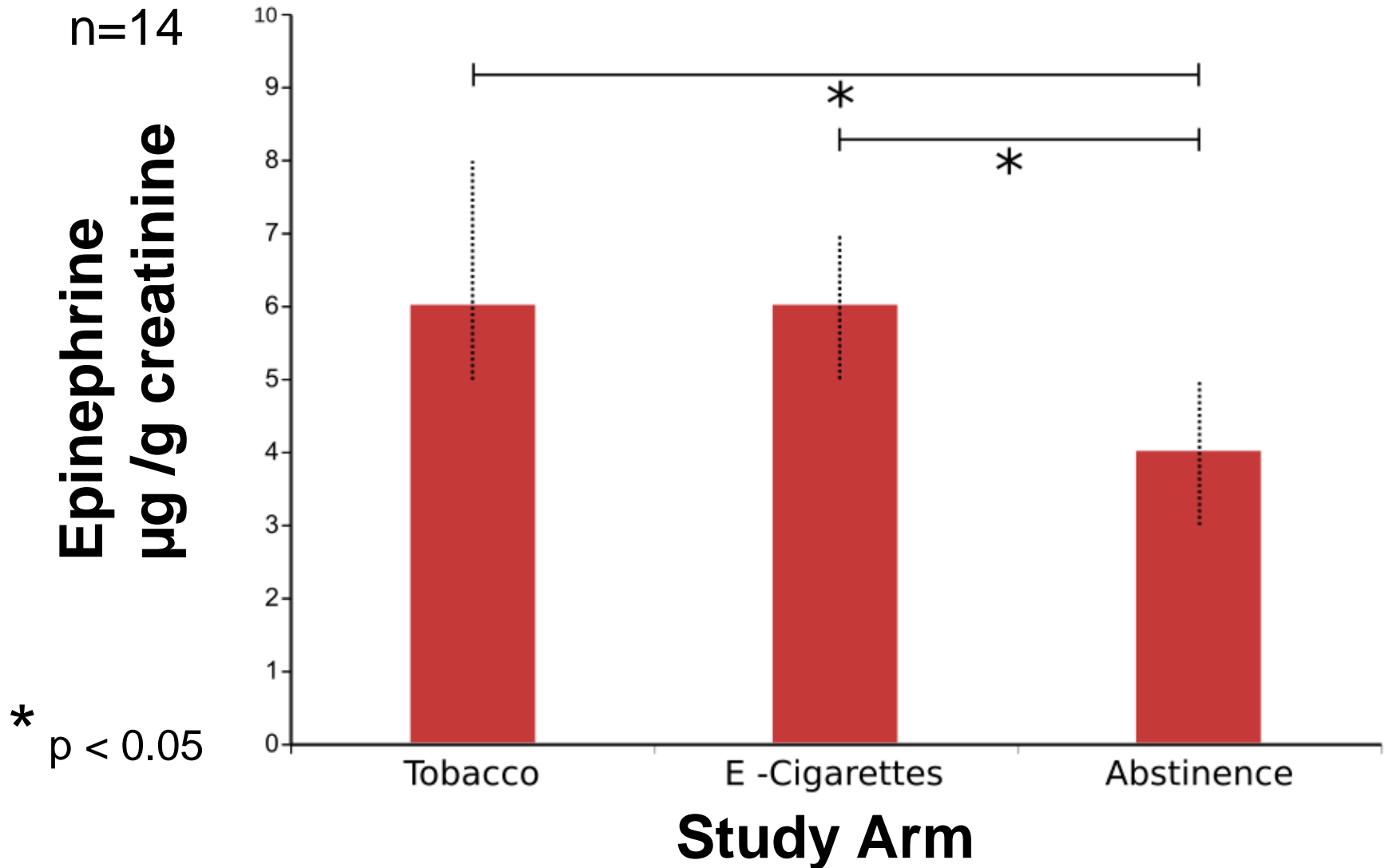
Probable Contribution

- **Probable**
- **Possible**
- **Unlikely**
- **Unlikely**
- **Probable**
- **Possible**
- **Possible**
- **Possible**

Mechanisms by which E-cigarettes could cause Acute CV Events



Epinephrine Excretion: Cigarette Smoking, E-Cigarettes, Abstinence



Health Effects of Smokeless Tobacco:

Natural Experiment on Effects of Nicotine without Combustion Toxicants

Snus Products

American snus



Swedish snus

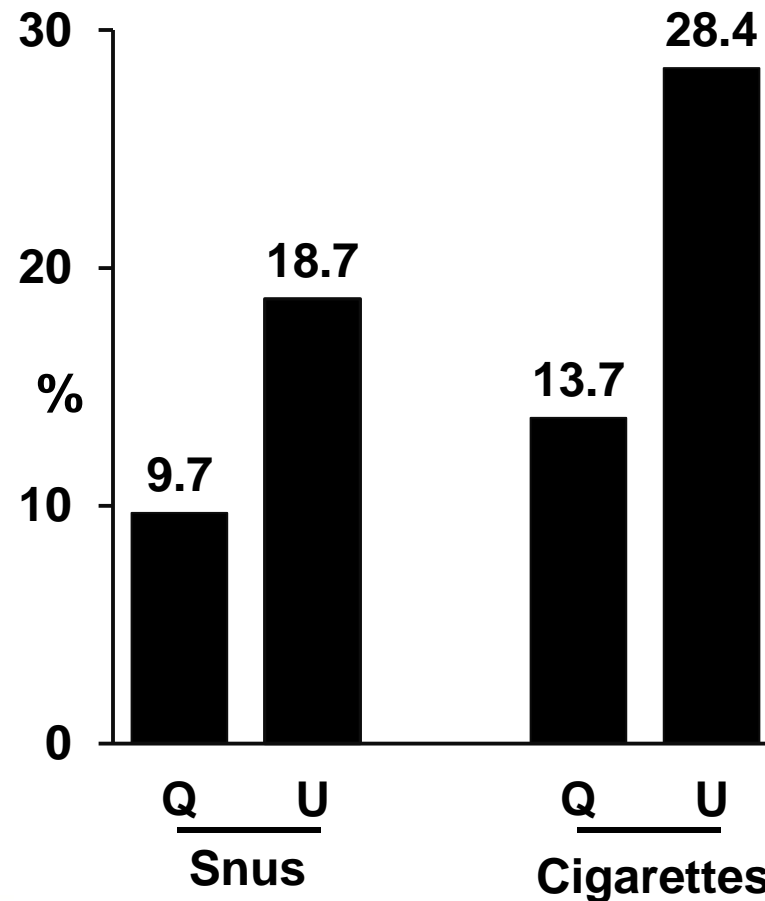


Smokeless tobacco and CVD: Swedish snus

- 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

Continued Snus Use After Myocardial Infarction Increases Mortality

Mortality (per 1000 pyr)



SWEDHEART MI register

2474 snus users - 27% Quit

6934 smokers – 61 % Quit

2 year follow up

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 is much less hazardous than smoking and replacing cigarettes with ANDS would be a substantial benefit for public health

Swedish Snus and Other Health Effects

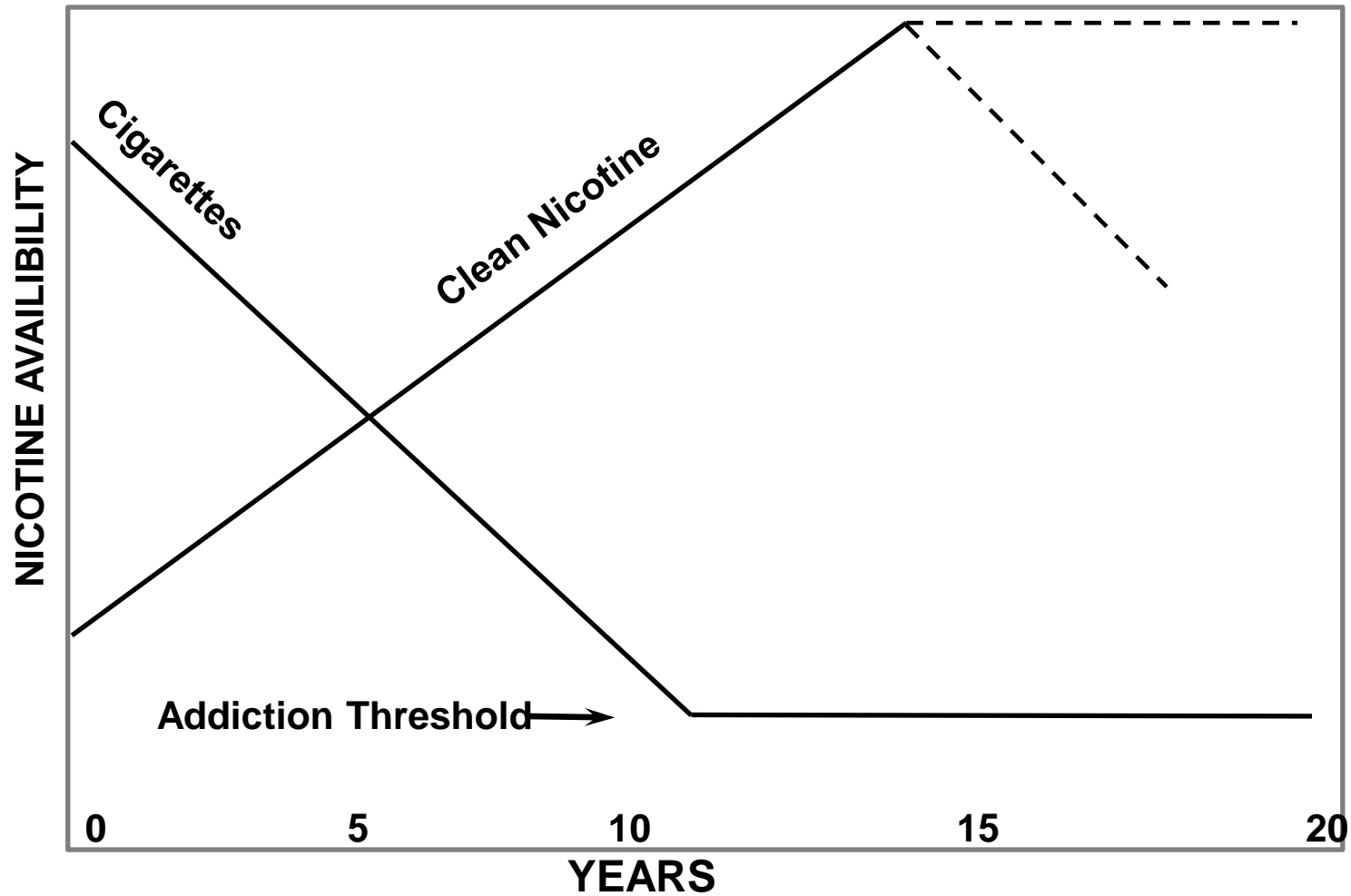
- Increase in pancreatic and esophageal, but not other cancers – likely nitrosamine effect
- Reproductive toxicity: higher risk of pre-eclampsia, reduced birth weight
- No increase in lung disease

Reduced Nicotine Content Cigarettes, E-cigarettes and the Cigarette End Game

Two approaches to reducing or eliminating the use of combusted tobacco products

- Reducing nicotine content of cigarettes to non-addicting levels
- Promoting the use of non-combusted forms of nicotine (such as NRT, ANDS)

Reducing Addictiveness of Cigarettes: A Nicotine Reduction Strategy



Clinical trials of reduced nicotine content cigarettes

- Smokers do not like RNC
- Smokers do reduce daily nicotine intake (by 65%), but 80% are not fully compliant with RNC
- Smokers of RNC seek alternative sources of nicotine in particular high reward value situations (such as first cigarette of day)

Concerns with free marketing of e-cigarettes for harm reduction

- Unlikely to out-compete conventional cigarettes
- Most EC users are dual users, with possible adverse effects on quitting smoking
- Attraction of youth and gateway to cigarettes
- Re-normalization of smoking-like behaviors

The complementary roles of nicotine reduction and non-combusted nicotine products

- ANDS provide ready availability of consumer-acceptable non-combusted nicotine to support shift away from nicotine from cigarettes
- Cigarette nicotine reduction not perceived as nicotine prohibition
- Dual use less likely because RNC are less satisfying and less desirable
- Gateway from EC to cigarettes for adolescents obviated because RNC minimally addictive

Regulatory context

- When faced with RNC many smokers may be motivated to quit smoking; and for those who continue to seek nicotine, ECs are likely the most acceptable alternative source
- The RNC cigarette and the emergence of attractive non-combusted nicotine products should be viewed as complementary components of a national intervention that could virtually end combusted tobacco use
- Regulations regarding ECs should focus on toxicity, safety and limiting youth access but should not disrupt features that make them a viable alternative to cigarettes, including (safe) flavors