Electronic Cigarettes, Nicotine and Policy Implications

Neal L Benowitz MD
University of California San Francisco

The E-Cigarette Summit
The Royal Society
London
November 17, 2016
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”
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

CIGARETTE SMOKING ➔ NICOTINE ABSORPTION ➔ AROUSAL MOOD MODULATION PLEASURE ➔ TOLERANCE AND PHYSICAL DEPENDENCE

CRAVING FOR NICOTINE TO SELF-MEDICATE WITHDRAWAL SYMPTOMS ➔ DRUG ABSTINENCE PRODUCES WITHDRAWAL SYMPTOMS
Nicotine pharmacokinetic profile differs by delivery system – could have implications for addiction and other toxicity
Nicotine PK with E-cigarette use during standardized session

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

(St. Helen, Addiction 2015)
Nicotine PK with ad libitum E-cigarette use

Plasma nicotine (ng/mL)

Time after first puff (min)

Subj 4, RBA

Subj 9, cartridge

UCSF Center for Tobacco Control Research and Education
“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)

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

<table>
<thead>
<tr>
<th>Action</th>
<th>Probable Contribution</th>
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<tr>
<td>Hemodynamic</td>
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<tr>
<td>Endothelial Dysfunction</td>
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<tr>
<td>Thrombogenesis</td>
<td>Unlikely</td>
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<tr>
<td>Inflammation</td>
<td>Unlikely</td>
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<tr>
<td>Arrhythmogenesis</td>
<td>Probable</td>
</tr>
<tr>
<td>Lipid Abnormalities</td>
<td>Possible</td>
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<tr>
<td>Insulin Resistance/Diabetes</td>
<td>Possible</td>
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<tr>
<td>Myocardial Effects</td>
<td>Possible</td>
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Mechanisms by which E-cigarettes could cause Acute CV Events

E-cigarette Aerosol

Oxidizing Chemicals
Particulates
Acrolein

Inflammation

Platelet Activation
Thrombosis

Endothelial Dysfunction

Coronary Vasoconstriction

Myocardial Demand for oxygen
and nutrients

Ventricular Arrhythmogenesis

Nicotine

Sympathetic Nervous System Activation
Catecholamine Release

↑ Heart Rate
↑ Blood Pressure
↑ Myocardial Contractility

Myocardial Ischemia
Myocardial Infarction

↓ Myocardial Blood Flow
Coronary Occlusion

Sudden Death
Epinephrine Excretion: Cigarette Smoking, E-Cigarettes, Abstinence

n=14

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Epinephrine μg/g creatinine</th>
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<tbody>
<tr>
<td>Tobacco</td>
<td>6.0 ± 1.2</td>
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<tr>
<td>E-Cigarettes</td>
<td>6.0 ± 1.2</td>
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<tr>
<td>Abstinence</td>
<td>4.0 ± 0.8</td>
</tr>
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* p < 0.05
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
Continued Snus Use After Myocardial Infarction Increases Mortality

SWEDHEART MI register
2474 snus users - 27% Quit
6934 smokers – 61 % Quit
2 year follow up

Mortality (per 1000 pyr)

<table>
<thead>
<tr>
<th></th>
<th>Snus</th>
<th>Cigarettes</th>
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<tr>
<td>Quit</td>
<td>9.7</td>
<td>13.7</td>
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<tr>
<td>U</td>
<td>18.7</td>
<td>28.4</td>
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(Arefalk, 2014)
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

NICOTINE AVAILIBILITY

YEARS

Cigarettes

Clean Nicotine

Addiction Threshold
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