Harms and Risks of Nicotine: Implications for Tobacco Harm Reduction

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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?
Nicotine-related Clinical Concerns

• Should the vaper who has switched from cigarette smoking to e-cigarettes be counseled to quit vaping? Are there high risk morbidities that warrant stopping nicotine sooner rather than later?
• 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
Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to “Nicotinic Cholinergic Receptors”
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

<table>
<thead>
<tr>
<th>Concern</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>Definite</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Probable</td>
</tr>
<tr>
<td>Reproductive Toxicity</td>
<td>Probable</td>
</tr>
<tr>
<td>Impaired Adolescent Brain</td>
<td>Possible</td>
</tr>
<tr>
<td>development</td>
<td></td>
</tr>
<tr>
<td>Infectious Disease Risk</td>
<td>Possible</td>
</tr>
<tr>
<td>Cancer</td>
<td>Possible</td>
</tr>
<tr>
<td>COPD</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>
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
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 across ECig products
Circadian Plasma Nicotine While Smoking Cigarettes or JUULing in Dual Users

#1

#2

#3

Plasma Nicotine (ng/ml)

Time of day

Combustible

Pod
E-Liquid nicotine concentrations do not predict daily nicotine exposure

<table>
<thead>
<tr>
<th>Nicotine Concentration</th>
<th>Blood/saliva Cotinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 mg/ml</td>
<td>430 ng/ml</td>
</tr>
<tr>
<td>22.5 mg/ml</td>
<td>316 ng/ml</td>
</tr>
<tr>
<td>59 mg/ml</td>
<td>172 ng/ml (50 – 313)</td>
</tr>
</tbody>
</table>
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)
The Splenocardiac Axis

THE SPLENOCARDIAC AXIS

Tobacco & Electronic Cigarettes

Nicotine

Oxidative Stress

↑ Sympathetic Nerve Activity

β3 Agonism

Bone Marrow

Leukocyte Progenitor

Pro-Inflammatory Monocytes

Coronary Artery Atheroma

Thrombus

Acute Myocardial Infarction

Middlekauff, TCVM, 2019
Health Effects of Smokeless Tobacco: Natural Experiment on Effects of Nicotine without Combustion Toxicants
Snus Products

Swedish snus

American snus

WARNING: This product is not a safe alternative to cigarettes.
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

Mortality (per 1000 pyr)

<table>
<thead>
<tr>
<th></th>
<th>Snus</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q</td>
<td>9.7</td>
<td>13.7</td>
</tr>
<tr>
<td>U</td>
<td>18.7</td>
<td>28.4</td>
</tr>
</tbody>
</table>

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
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

<table>
<thead>
<tr>
<th>Smoking, Snus and Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Small for Gestational Age</td>
</tr>
<tr>
<td>Preterm Delivery</td>
</tr>
<tr>
<td>Preeclampsia</td>
</tr>
</tbody>
</table>

Risk of Swedish Snuff Use (Snus) during Pregnancy

7000+ pregnant snus users

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>1.6</td>
<td>1.1-2.3</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.38</td>
<td>1.04-1.83</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1.11</td>
<td>0.97-1.28</td>
</tr>
</tbody>
</table>

Wikstrom et al. Epidemiology 21: 772, 2010
BJOG 117: 1005, 2010
Hypertension 55: 1100, 2010
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
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
Nicotine Impairs Clearance of Influenza Virus in Mice

Viral Load, qPCR

Days Post Infection

Failure to control the infection

mRNA Expression Relative to GAPDH

0 1 2 3

0 2 4 7

Failure of control at day 7/
mean of group at day 1

Control
VG/PG
VG/PG/Nicotine

Gotts, UCSF, 2019
Unpublished Data
Nicotine and Cancer

• Nicotine receptors on many cells, including tumor cells

• Demonstrated pathways by which nAChR activation could promote cancer (Grando, Nat Rev Cancer, 2015)

• Some evidence that nicotine can be nitrosated in vivo to form carcinogenic nitrosamines (Lee, PNAS, 2018) – unclear if dose is enough to cause cancer

• Sympathoadrenal activation (a nicotine effect) linked to carcinogenesis in animals. Beta adrenergic blocking drugs show protective effects in several cancers.
Nicotine and Cancer in People

• Swedish snus epidemiology finds no increased cancer risk, except possibly for pancreatic and esophageal cancers, which are likely nitrosamine related.

• Will take many years to determine if e-cigarettes are associated with cancer risk.
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.

• Nicotine is much less hazardous to cardiovascular health than smoking, but may contribute to acute CV events, particularly in the presence of CV disease.
Conclusions

• Nicotine is a reproductive hazard and should be avoided during pregnancy, unless it is used to support smoking cessation.

• 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.

• Because users titrate nicotine dose to desired effect, regulatory standards based on nicotine levels in non-combusted products is complicated. Higher nicotine products likely be safer due to less exposure to other chemicals that carry nicotine, but may also more addictive to adolescent non-smokers.