Overview of Harms and Risks of Nicotine

Neal L Benowitz MD
University of California San Francisco

Perspectives on Nicotine:
Science and Policy
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Disclosures

• Consultant to pharmaceutical companies that market smoking cessation products, including Pfizer and GlaxoSmithKline.

• Paid expert in litigation against tobacco companies.
Major Safety Concerns for Nicotine

- Addiction
- Cardiovascular Disease
- Reproductive Toxicity
- Infectious disease risk
- Cancer

- Definite
- Probable
- Probable
- Possible
- Unlikely
Pharmacologic Mechanisms
Nicotine Mimics the Neurotransmitter Acetylcholine:
Both Bind to “Nicotinic Cholinergic Receptors”
Structure of Nicotinic ACh Receptors

acetylcholine

pore

ion

muscle type nicotinic receptor

neuronal type nicotinic receptors

Picciotto M. Emerging neuronal nicotinic receptor targets. SRNT 9th Annual Meeting; February 2003; New Orleans, La.
Pharmacologic mechanisms by which nicotine might cause harm

<table>
<thead>
<tr>
<th>NACChR subtype</th>
<th>Effects</th>
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</thead>
<tbody>
<tr>
<td>α4β2*</td>
<td>Dopamine release, addiction, neuroplasticity</td>
</tr>
<tr>
<td>α3β4</td>
<td>Sympathetic stimulation, catecholamine release, CV toxicity</td>
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<tr>
<td>α7 homomeric</td>
<td>Endothelial dysfunction, angiogenesis, inhibition of apoptosis, anti-inflammation</td>
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</tbody>
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Caveat regarding in vitro studies-normal homeostatic mechanisms not operative
Nicotine pharmacokinetic profile differs by delivery system – could have implications for toxicity
Pharmacokinetics of Nicotine: tobacco products and nicotine gum

- Usual systemic dose from a cigarette is 1-2 mg
- Rate of rise is important determinant of intensity of effect
- Nicotine half-life 2 hrs
- Nicotine levels persist throughout the day and night with regular use
Nicotine PK with E-cigarette use during standardized session

Plasma nicotine (ng/mL)

Time after last of 15 puffs (min)

- 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) vs. Time after first puff (min)

- Subj 4, RBA
- Subj 9, cartridge
Cardiovascular Toxicity of Cigarette Smoking: What Role Nicotine?
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
How does cigarette smoking cause cardiovascular disease?

- Oxidative injury
- Endothelial damage and dysfunction
- Enhanced thrombosis
- Chronic inflammation
- Hemodynamic stress
- Adverse effects of blood lipids
- Insulin resistance and diabetes
- Reduced oxygen delivery by red blood cells
- Arrhythmogenesis
- Enhanced angiogenesis (?)
Constituents of tobacco smoke that contribute to CVD

- Oxidizing chemicals
- Carbon monoxide
- Volatile organic compounds
- Particulates
- Heavy metals
- Nicotine
How might Nicotine contribute to cardiovascular disease?

- Oxidative injury
- Endothelial damage and dysfunction
- Enhanced thrombosis
- Chronic inflammation
- Hemodynamic stress
- Adverse effects on blood lipids
- Insulin resistance and diabetes
- Reduced oxygen delivery by red blood cells
- Arrhythmogenesis
- Angiogenesis
Mechanisms of Smoking Induced Acute CV Events

- Oxidant chemicals
  - Particulates
  - Other combustion products
  - Inflammation
  - Platelet activation/thrombosis
    - Reduced myocardial blood, oxygen, and nutrient supply
    - Coronary occlusion
  - Endothelial dysfunction
    - Reducing myocardial blood, oxygen, and nutrient supply
    - Coronary occlusion

- Carbon monoxide
  - Reduced oxygen availability
  - Coronary vasoconstriction
    - Myocardial ischemia
    - Myocardial infarction
    - Sudden Death

- Nicotine
  - Sympathetic nervous system activation
    - Increased heart rate
    - Increased blood pressure
    - Increased myocardial contractility
    - Increased myocardial demand for oxygen and nutrients

- Increased myocardial demand for oxygen and nutrients

- Sudden Death
Cardiovascular Effects of Smokeless Tobacco: Natural Experiment on Health Effects of Nicotine without Combustion Toxicants
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)

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<tbody>
<tr>
<td>Snus</td>
<td>9.7</td>
<td>18.7</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>13.7</td>
<td>28.4</td>
</tr>
</tbody>
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(Arefalk, 2014)
Conclusions: Nicotine and Cardiovascular Disease

• Biological plausibility and epidemiological evidence that nicotine contributes to acute CV events
• Short term use poses little CV risk
• Long term use may be harmful in the presence of CVD
• Risk undoubtedly much lower than cigarette smoking
Conclusions: Nicotine and Reproductive Toxicity

• Cigarette smoking very toxic during pregnancy – maternal and fetal injury
• Possible adverse effect of nicotine on placental circulation
• Probable role of nicotine in SLT-induced pre-eclampsia
• Probable adverse effect of nicotine on fetal brain and lung development
• Risk undoubtedly less than cigarette smoking