Targeting Nicotine

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Brain Effects

- Nicotine targets nicotine receptors leading to the release of dopamine and other neurotransmitters.
- Cascade of neurotransmitters leads to reinforcing effects.
- Addiction potential is determined by rapidity and levels of nicotine delivery.

What if we target the reinforcing effects of nicotine?
Nicotine PK as a Therapeutic Target: Nicotine Vaccine

**Distribution**

- Reduce nicotine dose delivered to brain
- Slow rate of nicotine delivery to brain

**Elimination**

- Slower nicotine elimination

![Graph showing percentile groups ranked by Cmax Ab level over time](image)
Phase 3 Clinical Trial

![Graph showing Nicotine-specific Antibody mg/L vs Vaccine Dose (Placebo, 50 ug, 100 ug, 200 ug)]
Target the tobacco product!

Reduce nicotine in cigarettes to non-addictive levels.
VLNC Cigarettes: Effects on Smoking Amount and CO Exposure

Randomized smokers to:

- Very low nicotine content cigarettes: 0.05 mg yield
- Moderately reduced nicotine content cigarettes: 0.3 mg yield
- Nicotine lozenge

Hatsukami, Addiction, 2010
Effects on Dependence

Graph A: Changes in FTND scores over 6 weeks for different nicotine doses.
- 0.3 mg nicotine cigs (solid line with circles)
- 0.05 mg nicotine cigs (dashed line with squares)
- Nicotine lozenge (dotted line with triangles)

Graph D: Withdrawal symptoms over 12 weeks for different nicotine doses.
- 0.3 mg nicotine cigs (solid line with circles)
- 0.05 mg nicotine cigs (dashed line with squares)
- Nicotine lozenge (dotted line with triangles)
Effects on Abstinence

Time to replace and survival curves by treatment

Survival Probability

Time (days)
Adding NRT to VLNC Cigarettes: Effects on Study Cigarettes/Day and CO

Randomize smokers to:

- Very low nicotine content cigarettes (VLNC)
- Nicotine patch
- VLNC plus nicotine patch

Hatsukami, CEBP, 2013
Effects on Withdrawal Symptoms and Abstinence

No significant differences in continuous and point prevalence abstinence at 6 months.

VLNC + NP lower than NP, borderline lower than VLNC when switching to assigned products.
The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial

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Intervention vs. Control

**Median time to relapse:**
2mos vs. 2 weeks

**Continuous abstinence rate:**
23% vs. 15%; RR=1.50 95% CI 1.20,1.87
Regulation to reduce nicotine in cigarettes as a nation-wide policy

• Proposal:
  – A gradual reduction of nicotine content of cigarettes over 10-15 years.

• Goal:
  – To prevent nicotine addiction in youth

“New “end-game” strategies have been proposed with the goal of eliminating tobacco smoking. Some of these strategies may prove useful for the United States, particularly reduction of the nicotine yield of tobacco products to non-addictive levels.”
Current Dire Landscape

- Half million deaths per year
- 16 million with smoking-related disease
- About 40+ million smokers
Future More Desirable Landscape

Addictiveness/Appeal vs. Toxicity

Prescription??

Future More Desirable Landscape
• The **EVIDENCE** indicates that setting a maximum allowable nicotine content for all cigarettes could:

  – Reduce smoking **acquisition** and progress to addiction
  – Reduce the **prevalence** of smoking in a proportion of addicted smokers
  – Increase the **rate of quitting** and **reduce** the number of smokers who **relapse**
  – Increase the development, availability and use of **alternative forms of nicotine**, which have potential adverse effects but less that combusted products
Regulatory Recommendations

• Mandated reductions in nicotine to minimally addictive levels:
  – Should be supported by comprehensive regulations of all nicotine- and tobacco-containing products.
  – Must be a part of comprehensive tobacco control, including increased taxes on cigarettes, comprehensive smoking bans, educational campaigns and graphic warning labels or plain packaging.
  – Might be considered for all combusted products.
  – May be optimal if done immediately rather than gradually, for practical reasons, but must be preceded by health communication strategies and public education.
Regulatory Recommendations

• The availability of effective, affordable cigarette cessation treatment, alternative forms of nicotine, optimal medicinal forms of nicotine and other approved treatments and medicines for tobacco dependence and withdrawal will help dependent smokers.

• A strategy to reduce the addictiveness of tobacco is not recommended in the absence of developed capacity for market surveillance and product testing. Countries without adequate infrastructure...should carefully consider increasing that capacity before implementing such a strategy.
Impact of non-addictive cigarettes

“Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population”

Teng et al., Prev Med, 2005
Summary

• Very low nicotine content cigarettes could be an effective adjunct treatment (especially for women).

• A national policy of reducing nicotine content in cigarettes to minimally addictive levels could substantially improve public health.

• The benefits and risks of alternative nicotine products requires serious consideration.