- Tobacco and addiction research
- Where science meets policy and public health

Image source: Institute for Global Tobacco Control
Public Health Problem Comparisons

- Tobacco vs. other disease models
  - How does attempting to control tobacco addiction compare to attempting to control malaria?
  - HIV/AIDS?
Section A

Introduction to Tobacco Addiction
Objectives

- Discuss morbidity and mortality as side effects of addiction and how the biology of addiction impedes public health efforts

- Describe how tobacco products are designed to maximize addiction risk and how they have evolved over time to appear less harmful without actually reducing harm

- Demonstrate how tobacco marketing functions to initiate new cases and perpetuate existing cases of addiction
Objectives

- Evaluate how short- and long-range public health improvement can be aided by tobacco addiction prevention, cessation, and toxin reduction in continuing users

- Describe how the potential public health benefits of reduced toxicity products could be negated by the tobacco industry’s role in contributing to the initiation and perpetuation of addiction
Addiction Terminology

- Addiction—common term applied to maladaptive drug-seeking behavior (equivalent to American Psychiatric Association (APA)/World Health Organization (WHO) “dependence”)

- Dependence—APA refers to “nicotine” while WHO refers to “tobacco” amount delivered to organism

Image source: [http://www.nida.nih.gov/Published_Articles/Nicotinethreat.html](http://www.nida.nih.gov/Published_Articles/Nicotinethreat.html) retrieved 2/10/06
Addiction Terminology

- **Withdrawal**—transient symptoms following abstinence when physical dependence is present (i.e., neuroadaptation)

- **Tolerance**—decreased response to repeated doses

- **Dependence, withdrawal, and tolerance** can occur independently; withdrawal and tolerance are neither necessary nor sufficient for dependence
Addiction Terminology

- Abuse—maladaptive but also more “controlled”

- Abuse liability—refers to potential of a substance to lead to abuse or dependence due to central nervous system (CNS) effects
Tobacco Control Model of Nicotine Addiction

**Tobacco products**

**Agent**

**Environment**
social, cultural, political, economic, and historical factors

**Vector**
tobacco industry; other users

**Host**
smoker/chewer
incidental host: involuntary smoker

Drug Abuse and Addiction Modulated by Diverse Factors

- Drug (e.g., alcohol vs. nicotine vs. marijuana) and formulation (e.g., smoked vs. oral vs. injection; speed of release; sensory)

- Biological factors, including genetic, physiological, toxicological, and behavioral
Drug Abuse and Addiction Modulated by Diverse Factors

- Social factors, including cultural and ethnic; assumptions of normative behavior and perception of harm

- Environmental factors, including drug marketing (licit and illicit), music, media, access, and cost
Addictive drugs are diverse

Each produces a different profile of effects—e.g., alcohol is very intoxicating, opioids are soporific, and cocaine is stimulating
Drug Effects

- Key effects separate them from non-addictive drugs—psychoactive AND reinforcer for animals and humans, AND (usually) tolerance and withdrawal

- Addiction risk also varies widely
The Cocaine “Epidemic”

- DSM (Diagnostic and Statistical Manual of Mental Disorders) III (1980), which first listed “tobacco dependence” did not list cocaine dependence.

- Cocaine considered by many leading experts not to meet criteria for dependence/addiction.
The Cocaine “Epidemic”

- By *DSM IIIR* (1987), cocaine considered number one drug addiction problem
  - What happened?
  - Did molecule change or was there a genetic transformation?

- Availability, cost, social hype

- Cocaine got even more like cigarettes when crack discovered and “marketed”—unit doses conveniently packaged and smokable
Conventional Tobacco Products

1. 

![Image 1](http://www.cr.nps.gov/museum/exhibits/gettex/tobac2.htm)

2. 

![Image 2](http://www.cr.nps.gov/museum/exhibits/gettex/tobac2.htm)

3. 

![Image 3](http://www.genome.gov/17015035)

4. 

![Image 4](http://en.wikipedia.org/wiki/Cigar)

Photo by Dan Smith.

Extraordinary Product Diversity Beginning in the 1980s

Eclipse (R.J. Reynolds) 1990s
Ariva Cigaletts “Medical” Packaging

Projected Mortality Patterns

Tobacco-Related Deaths

Image source: National Institutes of Health
Smoking Camels

Image source: National Institutes of Health
Tobacco-Related Deaths

Image source: National Institutes of Health
Tobacco-Related Deaths

Image source: National Institutes of Health
Smoking and Pregnancy

Image source: National Institutes of Health
Smoking and Pregnancy

Image source: National Institutes of Health
Smoking and Pregnancy

Image source: National Institutes of Health
Cigarettes and other forms of tobacco are addictive

Nicotine is the drug in tobacco that causes addiction

Pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine
FDA Tobacco Rule (1996)

- Nicotine in cigarettes and smokeless tobacco is a drug
- Cigarettes and smokeless tobacco products are drug delivery devices
- Supported by pharmacology and secret documents from manufacturers
“Moreover, nicotine is addictive. We are, then, in the business of selling nicotine, an addictive drug . . .”

Addison Yeaman (1963)—Vice President and General Counsel of Brown and Williamson, a subsidiary of British American Tobacco
“I would be more cautious in using the pharmic-medical model—do we really want to tout cigarette smoking as a drug? It is, of course, but there are dangerous FDA implications to having such conceptualization go beyond these walls.”
A cigarette contains about 10 mg nicotine [no tar or carbon monoxide (CO)]

- Bioavailability—10–40%; typical dose is 1–2 mg per cigarette
- Bioavailability manipulated by ingredients, particle size engineering, and many other techniques

Tar or TPM—nicotine, water, and gas—not in tobacco (pyrolysis product); CO is a pyrolysis product
Effects of Nicotine—Beyond Chemical Structure

- Nicotine chemical structure
- Amount or dose
- Speed of delivery
  - $pK_a = 8.0$
- Sensory factors
- Other substances
Cigarettes
- Most toxic
- Most addictive
- Explosively fast delivery
- Optimal particle size
- pH controlled
- Sensory “optimization”
Tobacco-Delivered Nicotine

- Chemical cocktail
  - Ammonia increase dose and speed
  - Acetaldehyde synergy
  - Monoamine Oxidase (MAO) inhibiting effects
  - Additives reduce barriers
“No one has ever become a cigarette smoker by smoking cigarettes without nicotine.”
“It would appear that the increased smoker response is associated with nicotine reaching the brain more quickly . . .”
“AT [ammonia technology] is the key to competing in smoke quality with Philip Morris (PM) world-wide.”
“Increasing the pH of a medium in which nicotine is delivered increases the physiological effect of the nicotine by increasing the ratio of free base to acid salt form, the free base form being more readily transported across physiological membranes.”
Manipulating Nicotine in Cigarettes

- Nicotine content—tobacco type, plant part, addition
- Bioavailable nicotine (content, particle size, pH, temperature, moisture)
- Cheat FTC/ISO tests with vents, burn accelerants, filter overwrap
- Alter nicotine sensory impact by masking or unmasking
- Alter nicotine effects by altering speed of absorption (e.g., ammonia and other pH manipulations)
- Alter “nicotine” effects by synergy with other chemicals such as acetaldehyde and precursor sugars
Plasma Concentration after Smoking

Section B

Neurobiology of Nicotine
Like other abused drugs, nicotine stimulates reward pathways in the brain and increases dopamine in the nucleus accumbens.

Effects in the brain reinforce behavior, alter mood, and create a need that did not exist prior to drug exposure.
Most Nicotine Stays in the Body

Image source: National Institutes of Health
Blood Levels of Nicotine in Body

Image source: National Institutes of Health
Compensation to reduced nicotine often assumed

Actual data and industry documents indicate wide range of observed level and extent of compensation and determining conditions

Dose weaning strategies can be used to enable lasting reduction and cessation, in part by specific strategies to minimize compensation
Nicotine Compensation

- Could cigarettes be designed and accompanied by instructions and education to minimize compensation?

- Could cigarettes be designed to minimize adverse impact of compensation?
The Brain of a Smoker

Image source: National Institutes of Health
Effects of Four Drugs on Dopamine Levels

Effect of Acute Cocaine on Extracellular Dopamine

- Saline
- 0.3 mg/kg, IV
- 1.0 mg/kg, IV
- 3.0 mg/kg, IV

Dopamine (% of control)

Time (minutes)

Effect of Nicotine on Dopamine Release in the Shell of the Nucleus Accumbens

- 0.025 mg/kg IV dose
- 0.050 mg/kg IV dose

% of basal dopamine output

Time after nicotine (min)

Extracellular Dopamine in Rat Striatum After Acute IV D-Methamphetamine

- 5 mg/kg IV
- 2.5 mg/kg IV
- 1 mg/kg IV

Dopamine (nM)

Minutes

Release of Dopamine by Δ⁹-THC in the Shell of the Nucleus Accumbens

- 0.30 mg/kg IV dose
- 0.15 mg/kg IV dose

Percent of basal dopamine output

Minutes after Δ⁹-THC administration


Source: Melega et al., JPET 274:90-96, 1995

Brain Receptors

Image source: National Institutes of Health
Increased Number of Brain Receptors

Image source: National Institutes of Health
Hungry Brain Receptors

Image source: National Institutes of Health
Autopsy studies revealed up to 400% more nicotine binding sites in recently deceased smokers compared to nonsmokers—reversibility of such effects of nicotine exposure is uncertain.

Nicotine withdrawal is associated with dysfunction of the brain and performance—but it can be treated.
How Long to Recovery? Are All Brain Changes Reversible?

- Up to 400% increased receptors observed in some brain regions
- Tolerance can persist for a long time
- Sensitivity to craving-inducing smoke stimuli can persist for a long time
- Gradual reduction of nicotine and time to learn to live without nicotine is important for many people
Wide variation in effects, recovery, and capacity to compensate

What is normal for an adult nicotine-“treated” brain that was changed during its development and exposed to decades of nicotine exposure?

Will some need nicotine maintenance to sustain tobacco abstinence?
Addiction Risk in Ever Users

Other Effects Contribute to Tobacco Use

- Reduces anxiety and relieves stress and boredom
- Improves performance or at least reverses withdrawal deficits
- Decreases appetite
- Helps start car and answer phone?
Marketing Cigarettes

Image source: http://memory.loc.gov/ammem/awhhtml/awgc1/periodicals.html retrieved 2/9/06
Relapse

- Can be triggered by events such as . . .
  - Stress
  - Low doses of drugs of abuse
  - Drug-associated stimuli
    - Note that 10 puffs per cigarette x 20 cigarettes per day x 14 years > 1 million puffs
  - Advertising and marketing
    - 50 million other smokers provide ubiquitous smoking cues
Marketing Cigarettes

Image source: http://cancercontrol.cancer.gov/tcrb/monographs/5/m5_foreword.pdf retrieved 2/14/06
Marketing Cigarettes

Image source: http://www.cdc.gov/tobacco/sgr/sgr4kids/adbust.htm retrieved 2/14/06
Marketing Cigarettes

Image source: http://cancercontrol.cancer.gov/tcrb/monographs/13/m13_7.pdf retrieved 2/14/06
An Antismoking Ad

I miss my lung, Bob.

Image source: California Department of Health Services
Brown and Williamson (1979)

- Low tar cigarettes—
  - “Provide smokers with a choice and a reason not to quit.”
“Low tar,” “reduced,” “lowest,” “light,” “natural,” “no additives”

- These terms are regulated for other consumer products, including beer and potato chips

- They communicate reduced exposure

- They imply health benefits, and they SELL
1970s: Bluntly Stated Claims

Image source: http://cancercontrol.cancer.gov/tcrb/monographs/13/m13_7.pdf retrieved 2/14/06
“Claims” in the 21st century are more subtle due to consumer “education,” but are no less effective than the blunt claims of the 1970s.
Easily Covered Vents Provide Ventilation for the FTC

- Vents provide ventilation for the Federal Trade Commission but are easily covered by smokers.

- “Lighter” cigarettes are more ventilated and thus enable compensatory smoking.

FTC Rating System Options: A Misleading Marketing Tool

What should be done?

- Ban all labels implying health benefit
- Label nicotine—high, moderate, low, none
FTC Rating System Options: A Misleading Marketing Tool

- What should be done?
  - Require labels to show how to reduce intake
    - Smoke fewer cigarettes
    - Take fewer puffs
    - Leave longer butts
    - Check butts for stain size and darkness
Knowing the science of tobacco addiction is as useful for stopping the spread of the disease as knowing how mosquitoes carry and spread malaria has been vital to its control . . .
Fighting Tobacco Addiction

- Just as knowing how mosquitoes carry and spread malaria has been vital to its control...
  
  - The science of nicotine is vital to controlling the tobacco epidemic
  
  - Preventing and treating tobacco dependence is like preventing and treating malaria in a mosquito-infested swamp
  
  - Or cocaine dependence in a crack-infested neighborhood
Spheres of Influence Making Treatment Fit

Source: Modified from Pentz, M. A. University of Southern California.
Dependence usually develops in adolescence
Most smokers are dependent
In U.S. two-thirds of youth try tobacco and one-third to one-half “graduate”
Tobacco dependence is more than nicotine—tobacco delivered nicotine (TDN)
All forms of nicotine are not equally interchangeable
Tobacco Dependence Facts to Consider

- Diversity in needs and “benefits”—weight, cognition, mood, withdrawal relief, social “tool,” coupons
- 20 cigarettes per day = 200 puffs (i.e., 200 “doses” per day)
- Urge surge easily leads to relapse
- Relatively little “aging” related cessation
- Population diversity—gender, ethnic, geographic
- Ubiquitous marketing and availability of tobacco
Pharmacological Treatment for Tobacco Dependence

- Gum and lozenge—two and four mg (deliver one and two mg)
- Nasal spray—one mg/two squirts
- Oral inhaler—about 0.01 mg/puff
- Patch—0.9 mg per hour for 16 or 24 hours
- Bupropion—150–300 mg/day
Blood Levels of Nicotine by Delivery Method

Fighting Biology (Addiction)

- Nicotine exposed brain finds reasons not to quit and reasons to fear treatment
- Nicotine exposed brain likes fast nicotine hits—not slow safe nicotine
- Nicotine exposed brain may never allow the person to feel right or function right without nicotine
- Medications make it possible, not easy, to quit smoking
FDA Dual Strategy—1996

- Prevention—1996 Tobacco Rule
  - Reduce access—restrictions on sales
  - Reduce appeal—restrictions on advertising and other marketing approaches
  - Treatment—over-the-counter gum and patch available in 1996
  - Increase access
  - Increase appeal by highly regulated marketing

- 2000
  - Supreme court ruled against FDA authority
  - FDA does not have the authority; Congress does
Tobacco from addiction to the FDA’s attempt to regulate it
Nicotine is the addictive drug in tobacco
But tobacco addiction involves more than just nicotine
The tobacco industry has engineered products to increase addictiveness
Marketing helps spread tobacco addiction