NICOTINE PHARMACOLOGY and PRINCIPLES of ADDICTION
Cigarettes and other forms of tobacco are addicting.

Nicotine is the drug in tobacco that causes addiction.

The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.

CHEMISTRY of NICOTINE

*Nicotiana tabacum*

Natural liquid alkaloid
Colorless, volatile base $pK_a = 8.0$
PHARMACOLOGY

Pharmacokinetics
Effects of the body on the drug
- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamics
Effects of the drug on the body
Absorption is pH dependent

- **In acidic media**
  - Ionized $\Rightarrow$ poorly absorbed across membranes

- **In alkaline media**
  - Nonionized $\Rightarrow$ well absorbed across membranes
  - At physiologic pH (7.4), $\sim$31% of nicotine is nonionized

**At physiologic pH, nicotine is readily absorbed.**
NICOTINE ABSORPTION: BUCCAL (ORAL) MUCOSA

The pH inside the mouth is 7.0.

**Acidic media**
(limited absorption)
Cigarettes

**Alkaline media**
(significant absorption)
Pipes, cigars, spit tobacco, oral nicotine products

Beverages can alter pH, affect absorption.
Nicotine is readily absorbed through intact skin.

Nicotine is well absorbed in the small intestine but has low bioavailability (20-45%) due to first-pass hepatic metabolism.
Nicotine is “distilled” from burning tobacco and carried in tar droplets. Nicotine is rapidly absorbed across respiratory epithelium.
- Lung pH = 7.4
- Large alveolar surface area
- Extensive capillary system in lung

Approximately 1 mg of nicotine is absorbed from each cigarette.
Nicotine reaches the brain within 10–20 seconds.

NICOTINE METABOLISM

70–80% cotinine

~ 10% other metabolites

Metabolized and excreted in urine

10–20% excreted unchanged in urine

NICOTINE EXCRETION

- **Half-life**
  - Nicotine $t_{1/2} = 2$ hr
  - Cotinine $t_{1/2} = 16$ hr

- **Excretion**
  - Occurs through kidneys (pH dependent; ↑ with acidic pH)
  - Through breast milk
Nicotine binds to receptors in the brain and other sites in the body. Nicotine has predominantly stimulatory effects.
NICOTINE PHARMACODYNAMICS (cont’d)

Central nervous system
- Pleasure
- Arousal, enhanced vigilance
- Improved task performance
- Anxiety relief

Cardiovascular system
- ↑ Heart rate
- ↑ Cardiac output
- ↑ Blood pressure
- Coronary vasoconstriction
- Cutaneous vasoconstriction

Other
- Appetite suppression
- Increased metabolic rate
- Skeletal muscle relaxation
NEUROCHEMICAL and RELATED EFFECTS of NICOTINE

- **Dopamine** → Pleasure, appetite suppression
- **Norepinephrine** → Arousal, appetite suppression
- **Acetylcholine** → Arousal, cognitive enhancement
- **Glutamate** → Learning, memory enhancement
- **Serotonin** → Mood modulation, appetite suppression
- **β-Endorphin** → Reduction of anxiety and tension
- **GABA** → Reduction of anxiety and tension

WHAT IS ADDICTION?

“Compulsive drug use, without medical purpose, in the face of negative consequences”

Alan I. Leshner, Ph.D.
Former Director, National Institute on Drug Abuse
National Institutes of Health

Nicotine addiction is a chronic condition with a biological basis.
Nicotine enters the brain, stimulating nicotine receptors. This leads to dopamine release, which activates the DOPAMINE REWARD PATHWAY. The pathway includes the Prefrontal cortex, Nucleus accumbens, Ventral tegmental area, and other brain regions. The process is a key component in understanding addiction and reward mechanisms.
Human smokers have increased nicotine receptors in the prefrontal cortex.

Image courtesy of George Washington University / Dr. David C. Perry

NICOTINE PHARMACODYNAMICS: WITHDRAWAL EFFECTS

- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness/impatience
- Depressed mood/depression
- Insomnia
- Impaired performance
- Increased appetite/weight gain
- Cravings

Most symptoms manifest within the first 1–2 days, peak within the first week, and subside within 2–4 weeks.

NICOTINE ADDICTION CYCLE

NICOTINE ADDICTION

- Tobacco users maintain a minimum serum nicotine concentration in order to
  - Prevent withdrawal symptoms
  - Maintain pleasure/arousal
  - Modulate mood

- Users self-titrate nicotine intake by
  - Smoking/dipping more frequently
  - Smoking more intensely
  - Obstructing vents on low-nicotine brand cigarettes

ASSESSING NICOTINE DEPENDENCE

Fagerström Test for Nicotine Dependence (FTND)

- Developed in 1978 (8 items); revised in 1991 (6 items)

- Most common research measure of nicotine dependence; sometimes used in clinical practice

- Responses coded such that higher scores indicate higher levels of dependence

- Scores range from 0 to 10; score of greater than 5 indicates substantial dependence

Though expensive, hiring a professional actor dressed as death to stalk his every move finally broke Ted of his smoking addiction.
FACTORS CONTRIBUTING to TOBACCO USE

**Individual**
- Sociodemographics
- Genetic predisposition
- Coexisting medical conditions

**Environment**
- Tobacco advertising
- Conditioned stimuli
- Social interactions

**Pharmacology**
- Alleviation of withdrawal symptoms
- Weight control
- Pleasure, mood modulation

Tobacco Use
TOBACCO DEPENDENCE: A 2-PART PROBLEM

**Physiological**
- The addiction to nicotine
  - Treatment
  - Medications for cessation

**Behavioral**
- The habit of using tobacco
  - Treatment
  - Behavior change program

Treatment should address the physiological **and** the behavioral aspects of dependence.
NICOTINE PHARMACOLOGY and ADDICTION: SUMMARY

- Tobacco products are effective delivery systems for the drug nicotine.
- Nicotine is a highly addictive drug that induces a constellation of pharmacologic effects, including activation of the dopamine reward pathway in the brain.
- Tobacco use is complex, involving the interplay of a wide range of factors.
- Treatment of tobacco use and dependence requires a multifaceted treatment approach.