



NICOTINE PHARMACOLOGY and PRINCIPLES of ADDICTION



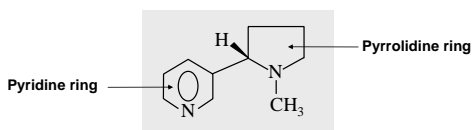
NICOTINE ADDICTION U.S. Surgeon General's Report (1988)

- 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.

U.S. Department of Health and Human Services. (1988). *The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General.*



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



NICOTINE ABSORPTION

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 (7.3–7.5), ~31% of nicotine is unionized

**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 ABSORPTION: SKIN and GASTROINTESTINAL TRACT

- Nicotine is readily absorbed through intact skin.
- Nicotine is well absorbed in the small intestine but has low bioavailability (30%) due to first-pass hepatic metabolism.



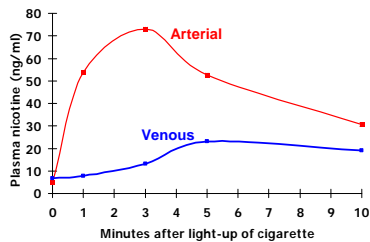
NICOTINE ABSORPTION: LUNG

- 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



NICOTINE DISTRIBUTION

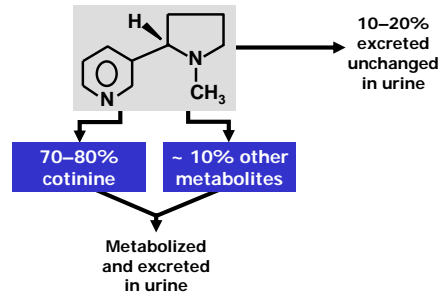
Nicotine reaches the brain within 11 seconds.



Henningfield et al. (1993). *Drug Alcohol Depend* 33:23-29.



NICOTINE METABOLISM



Adapted and reprinted with permission, Benowitz et al. (1994). *J Pharmacol Exp Ther* 268:296-303.



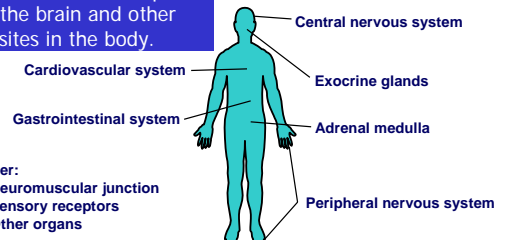
NICOTINE EXCRETION

- Half-life
 - Nicotine $t_{1/2} = 2$ hr
 - Cotinine $t_{1/2} = 19$ hr
- Excretion
 - Occurs through kidneys (pH dependent; \uparrow with acidic pH)
 - Through breast milk



NICOTINE PHARMACODYNAMICS

Nicotine binds to receptors in the brain and other sites in the body.



Nicotine has predominantly stimulant 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

N I C O T I N E	→ Dopamine	→ Pleasure, reward
	→ 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

Benowitz, (1999). *Nicotine Tob Res* 1(Suppl):S159-S163.

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

BIOLOGY of NICOTINE ADDICTION: ROLE of DOPAMINE

Nicotine stimulates dopamine release

Pleasurable feelings

Repeat administration

Tolerance develops

Nicotine addiction is *not* just a bad habit.
Discontinuation leads to withdrawal symptoms.

DOPAMINE REWARD PATHWAY

Prefrontal cortex

Dopamine release

Nucleus accumbens

Ventral tegmental area

Stimulation of nicotine receptors

Nicotine enters brain

CHRONIC ADMINISTRATION of NICOTINE: EFFECTS on the BRAIN

Human smokers have increased nicotine receptors in the prefrontal cortex.

High

Low

Nonsmoker Smoker

Image courtesy of George Washington University / Dr. David C. Perry
Perry et al. (1999). *J Pharmacol Exp Ther* 289:1545-1552.



NICOTINE PHARMACODYNAMICS: WITHDRAWAL EFFECTS

- Depression
- Insomnia
- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite/weight gain
- Decreased heart rate
- Cravings*

Most symptoms peak 24–48 hr after quitting and subside within 2–4 weeks.

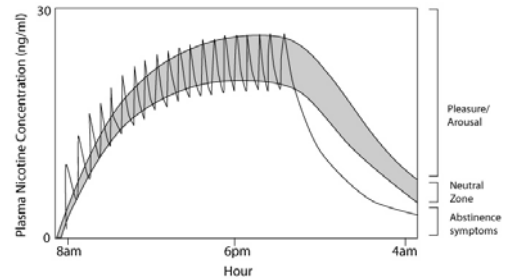
HANDOUT

* Not considered a withdrawal symptom by DSM-IV criteria.

American Psychiatric Association. (1994). DSM-IV.
 Hughes et al. (1991). *Arch Gen Psychiatry* 48:52–59
 Hughes & Hatsukami. (1998). *Tab Control* 7:92–93.



NICOTINE ADDICTION CYCLE



Reprinted with permission. Benowitz. (1992). *Med Clin N Am* 2:415–437.



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

HANDOUT

Heatherton et al. (1991). *British Journal of Addiction* 86:1119–1127.



FACTORS CONTRIBUTING TO TOBACCO USE

Environment

- Tobacco advertising
- Conditioned stimuli
- Social interactions

Physiology

- Genetic predisposition
- Coexisting medical conditions

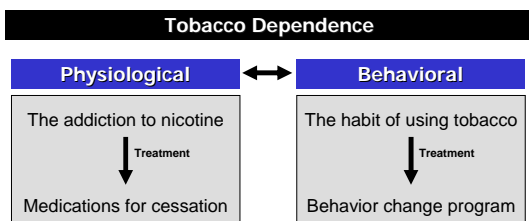


Pharmacology

- Alleviation of withdrawal symptoms
- Weight control
- Pleasure



TOBACCO DEPENDENCE: A 2-PART PROBLEM



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.
- Nicotine activates the **dopamine reward pathway** in the brain, which reinforces continued tobacco use.
- Tobacco users who are dependent on nicotine **self-regulate tobacco** intake to maintain pleasurable effects and prevent withdrawal.



NICOTINE PHARMACOLOGY and ADDICTION: SUMMARY (cont'd)

- Nicotine dependence is a form of **chronic brain disease**.
- Tobacco use is a **complex disorder** involving the interplay of the following:
 - Pharmacology of nicotine (pharmacokinetics and pharmacodynamics)
 - Environmental factors
 - Physiologic factors
- Treatment of tobacco use and dependence requires a **multifaceted treatment approach**.