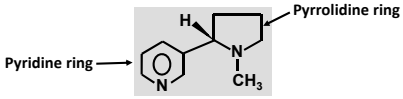
NICOTINE PHARMACOLOGY and PRINCIPLES of ADDICTION

NICOTINE ADDICTION
U.S. Surgeon General's Report

- 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 ➲ poorly absorbed across membranes
- In alkaline media
  - Nonionized ➲ well absorbed across membranes
  - At physiologic pH (7.4), ~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)	**Alkaline media** (significant absorption)
Cigarettes	Pipes, cigars, spit tobacco, oral nicotine products

Beverages can alter pH, affect absorption.

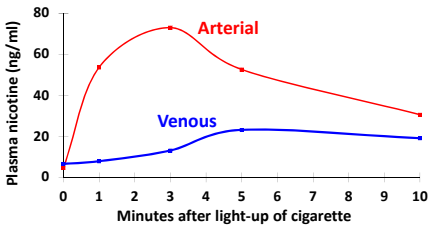
NICOTINE ABSORPTION: SKIN and GASTROINTESTINAL TRACT

- Nicotine is readily absorbed through intact skin.
- Nicotine is well absorbed in the small intestine
  - Low bioavailability (20-45%) due to first-pass hepatic metabolism.

NICOTINE ABSORPTION: LUNG

- Nicotine is "distilled" from burning tobacco
- Carried in tar droplets to the lungs
- Nicotine is rapidly absorbed across respiratory epithelium
  - Lung pH = 7.4
  - Large alveolar surface area
  - Extensive capillary system
- Approximately 1-2 mg of nicotine is absorbed from each cigarette

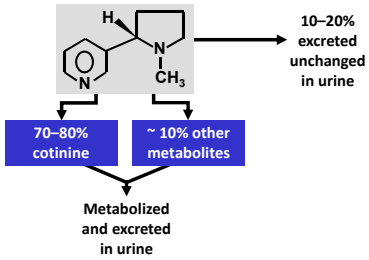
NICOTINE DISTRIBUTION



Nicotine reaches the brain within 10–20 seconds.

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

NICOTINE METABOLISM



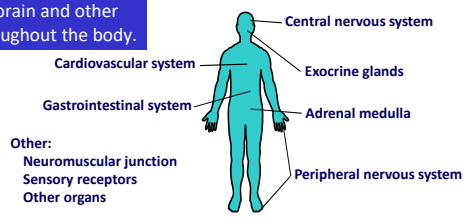
Adapted and reprinted with permission. Benowitz et al. (1994). *J Pharmacol Exp Ther* 268:296–303.

NICOTINE EXCRETION

- Half-life
  - Nicotine $t_{½}$ = 2 hr
  - Cotinine $t_{½}$ = 16 hr
- Excretion
  - Occurs through kidneys (pH dependent; ↑ with acidic pH)
  - Through breast milk

NICOTINE PHARMACODYNAMICS

Nicotine binds to receptors in the brain and other sites throughout 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

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

Benowitz. (2008). *Clin Pharmacol Ther* 83:531–541.

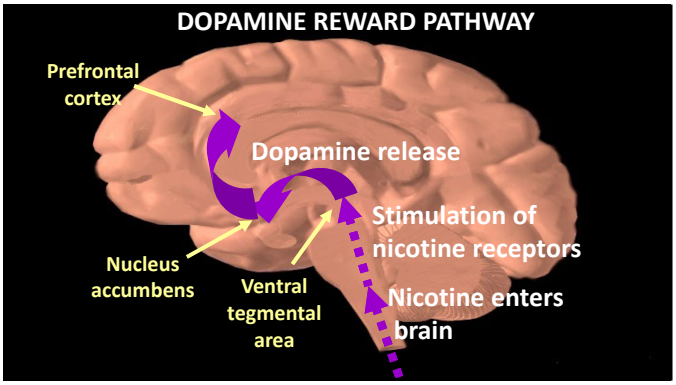
WHAT IS ADDICTION?

"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.

DOPAMINE REWARD PATHWAY



CHRONIC ADMINISTRATION of NICOTINE: EFFECTS on the BRAIN

Human smokers have increased nicotine receptors in the prefrontal cortex.

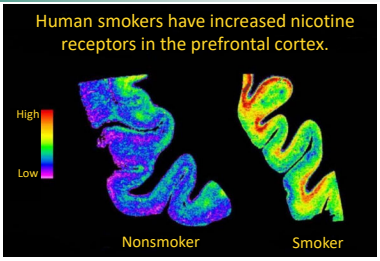
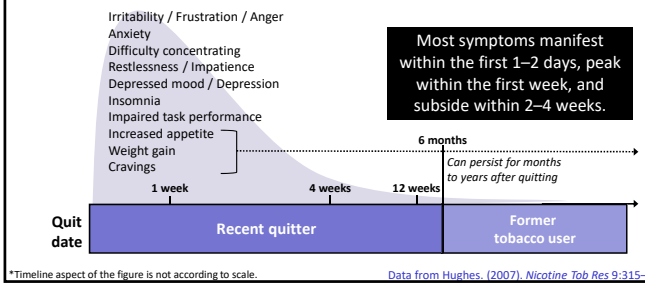


Image courtesy of George Washington University / Dr. David C. Perry
Perry et al. (1999) *J Pharmacol Exp Ther* 289:1545–1552.

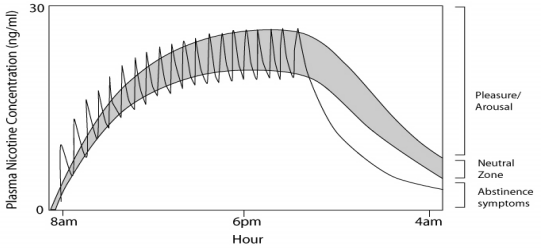
NICOTINE WITHDRAWAL SYMPTOMS: Time Course*



*Timeline aspect of the figure is not according to scale.

Data from Hughes. (2007). *Nicotine Tob Res* 9:315–327.

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/vaping more frequently
  - Smoking/vaping more intensely

Benowitz. (2008). *Clin Pharmacol Ther* 83:531–541.

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 suggest higher levels of dependence
- Scores range from 0 to 10; score of greater than 5 suggest substantial dependence

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

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FACTORS CONTRIBUTING to TOBACCO USE

Individual
- Sociodemographics
- Genetic predisposition
- Coexisting medical conditions

Tobacco Use

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

Environment
- Tobacco advertising
- Conditioned stimuli
- Social interactions

TOBACCO DEPENDENCE: A 2-PART PROBLEM

Tobacco Dependence

Physiological	Behavioral
The addiction to nicotine	The habit of using tobacco
↓ Treatment	↓ Treatment
Medications for cessation	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.