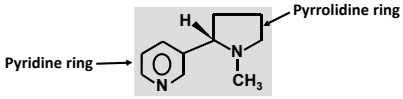
NICOTINE PHARMACOLOGY and PRINCIPLES of ADDICTION

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.

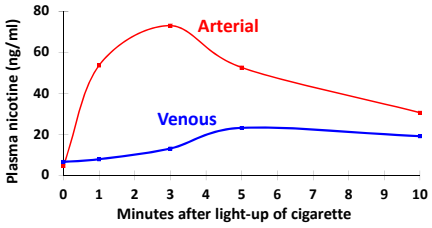
NICOTINE ABSORPTION: SKIN and GASTROINTESTINAL TRACT

- 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 mg of nicotine is absorbed from each cigarette

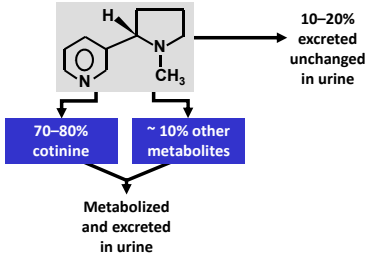
NICOTINE DISTRIBUTION



Nicotine reaches the brain within 10–20 seconds.

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

NICOTINE METABOLISM



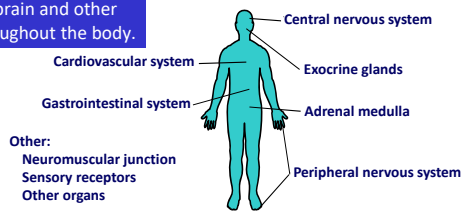
Adapted and reprinted with permission. Benowitz et al. (1994). *J Pharmacol Exp Ther* 268:296–303.

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

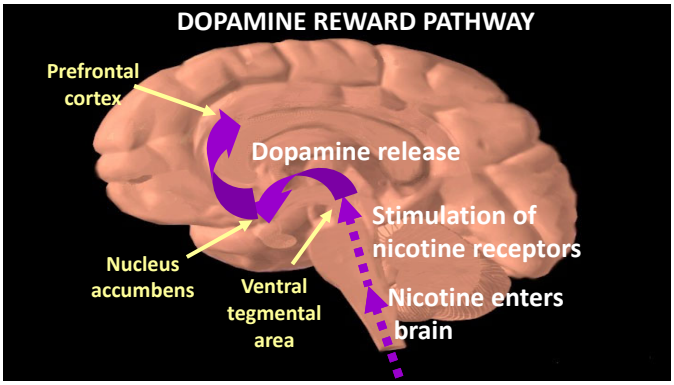
Benowitz. (2008). *Clin Pharmacol Ther* 83:531–541.

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.



CHRONIC ADMINISTRATION of NICOTINE: EFFECTS on the BRAIN

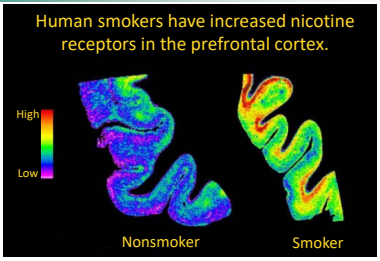
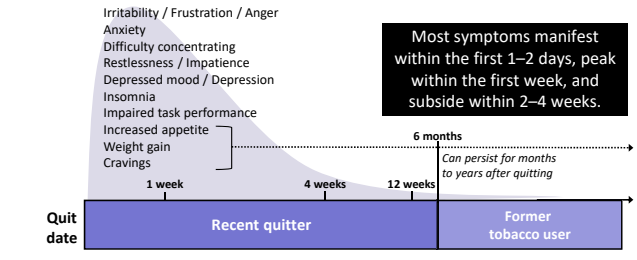


Image courtesy of George Washington University / Dr. David C. Perry
Perry et al. (1999). *J Pharmacol Exp Ther* 289:1545–1552.

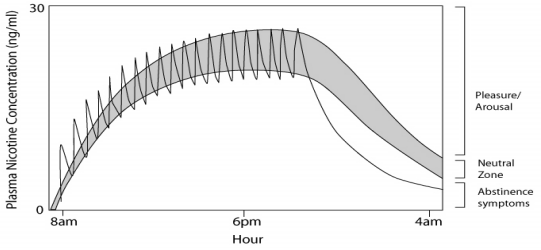
NICOTINE WITHDRAWAL SYMPTOMS: Time Course*



*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 more frequently
  - Smoking more intensely
  - Obstructing vents on low-nicotine brand cigarettes

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

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

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.

DRUG INTERACTIONS with TOBACCO SMOKE

PHARMACOKINETIC DRUG INTERACTIONS with TOBACCO SMOKE

Drugs that may have a *decreased effect* due to induction of CYP1A2:

- Bendamustine
- Caffeine
- Clozapine
- Erlotinib
- Fluvoxamine
- Haloperidol
- Olanzapine
- Pirfenidone
- Riociguat
- Ropinirole
- Tasimelteon
- Theophylline
- Irinotecan (clearance increased and systemic exposure decreased, due to increased glucuronidation of its active metabolite)

Smoking cessation will reverse these effects.

DRUG INTERACTION: TOBACCO SMOKE and CAFFEINE

- Constituents in tobacco smoke induce CYP1A2 enzymes, which metabolize caffeine
  - Caffeine levels increase ~56% upon quitting
- Challenges:
  - Nicotine withdrawal effects might be enhanced by increased caffeine levels
  - Insomnia can be due to ↑ caffeine levels or a side effect of a smoking cessation drug (e.g., varenicline or bupropion)
- Decrease caffeine intake by about half when quitting
- For individuals with a typical bedtime, suggest eliminating caffeine by early afternoon

PHARMACODYNAMIC DRUG INTERACTIONS with TOBACCO SMOKE

Smokers who use combined hormonal contraceptives have an increased risk of serious cardiovascular adverse effects:

- Stroke
- Myocardial infarction
- Thromboembolism

This interaction **does not** decrease the efficacy of hormonal contraceptives.

Women who are 35 years of age or older AND smoke at least 15 cigarettes per day are at significantly elevated risk.

DRUG INTERACTIONS WITH TOBACCO SMOKE

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke interacts with medications through pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). Smokers may require higher doses of medications that are CYP1A2 substrates. Upon cessation, dose reductions might be needed. PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established, and the assumption is that any smoker is susceptible to the same degree of interaction. **The most clinically significant interactions are depicted in the shaded rows.**

Drug/Class	Mechanism of Interaction and Effects
Pharmacokinetic Interactions	
Alprazolam (Xanax®)	▪ Conflicting data on significance, but possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Bendamustine (Treanda®)	▪ Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers due to likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.
Caffeine	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). Caffeine levels likely ↑ after cessation.
Chlorpromazine (Thorazine®)	▪ ↓ Area under the curve (AUC) (36%) and serum concentrations (24%). ▪ ↓ Sedation and hypotension possible in smokers; smokers may require ↑ dosages.
Clopidogrel (Plavix®)	▪ ↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite. ▪ Enhanced response to clopidogrel in smokers (≥10 cigarettes/day): ↑ platelet inhibition, ↓ platelet aggregation; improved clinical outcomes have been shown (smokers' paradox; may be dependent on CYP1A2 genotype); tobacco cessation should still be recommended in at-risk populations needing clopidogrel.
Clozapine (Clozaril®)	▪ ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (by 18%). ▪ ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.
Erlotinib (Tarceva®)	▪ ↑ Clearance (24%); ↓ trough serum concentrations (2-fold).

The shaded rows indicate clinically significant drug interactions.

DRUG INTERACTIONS with TOBACCO SMOKE: SUMMARY

Clinicians should be aware of their patients' smoking status:

- Clinically significant interactions result the combustion products of tobacco smoke, not from nicotine.
- Constituents in tobacco smoke (e.g., polycyclic aromatic hydrocarbons; PAHs) may enhance the metabolism of other drugs, resulting in an altered pharmacologic response.
- Changes in smoking status might alter the clinical response to the treatment of a wide variety of conditions.
- Drug interactions with smoking should be considered when patients start smoking, quit smoking, or markedly alter their levels of smoking.