NICOTINE PHARMACOLOGY and PRINCIPLES of ADDICTION

CHEMISTRY of NICOTINE

Nicotiana tabacum
Natural liquid alkaloid
Colorless, volatile base $pK_a = 8.0$

PHARMACOLOGY

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.


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 (7.4), $\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.

<table>
<thead>
<tr>
<th>pH Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidic media (limited absorption)</td>
<td>Cigarettes</td>
</tr>
<tr>
<td>Alkaline media (significant absorption)</td>
<td>Pipes, cigars, spitz tobacco, oral nicotine products</td>
</tr>
</tbody>
</table>

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.


NICOTINE METABOLISM


NICOTINE EXCRETION

- Half-life
  - Nicotine $t_{1/2} = 2$ hr
  - Cotinine $t_{1/2} = 16$ 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 throughout the body.

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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.

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

NICOTINE WITHDRAWAL SYMPTOMS: Time Course*

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


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NICOTINE ADDICTION CYCLE

- 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

FACTORS CONTRIBUTING to TOBACCO USE

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

<table>
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<th>Tobacco Dependence</th>
<th>Treatment</th>
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<tbody>
<tr>
<td><strong>Physiological</strong></td>
<td>Medications for cessation</td>
</tr>
<tr>
<td>The addiction to nicotine</td>
<td>Treatment</td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
<td>Behavior change program</td>
</tr>
<tr>
<td>The habit of using tobacco</td>
<td></td>
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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.
PHARMACOKINETIC DRUG INTERACTIONS with TOBACCO SMOKE

Drugs that may have a decreased effect due to induction of CYP1A2:
- Bendamustine
- Caffeine
- Clozapine
- Erlotinib
- Fluvoxamine
- Irinotecan (clearance increased and systemic exposure decreased, due to increased glucuronidation of its active metabolite)

Smoking cessation will reverse these effects.

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:

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

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.

The shaded rows indicate clinically significant drug interactions.

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