Psychostimulants produce:
• Increases in alertness.
• Behavioral arousal.
  • Activation of sympathetic nervous system.
    • Sympathomimetic Effects

Tobacco and Nicotine
Tobacco

- Native Americans were the first to utilize tobacco.
- Columbus discovered tobacco in the new world.
- Tobacco use spread rapidly through Europe.

Tobacco Preparations

- Smoking Tobacco
- Chewing Tobacco
- Snuff

Active ingredient is nicotine.
- Named after *Nicotiana*.
- Found only in tobacco.

Behavioral / Physiological Effects of Nicotine

- Pleasure/Euphoria
- Sympathomimetic effects.
- Increases in alertness.
  - Maybe overestimated?
- Appetite Suppressant/Nausea
- Muscle Tremor

- Nesbitt’s Paradox
Pharmacokinetics
Inhalation Absorption
• Very rapid absorption.
• One cigarette contains 1-5 mg nicotine.
• A smoker utilizes ≈1 mg of this nicotine.
  • Dose control is important.
  • Low tar/nicotine cigarettes?

Oral/Nasal Absorption
• Nicotine is basic, so G.I. tract absorption is poor.
• Cigarette smoke makes the saliva acidic.
  • Nicotine poorly absorbed in mouth.
• Pipe and cigar smoke isn’t acidic.
  • Nicotine easily absorbed in mouth.
• Nicotine from chewed tobacco and snuff absorbed through oral/nasal membranes.

Nicotine easily crosses the blood brain barrier.

Metabolism
• 80-90% metabolized by the liver.
• Remainder secreted in urine.
• Half-life of ≈1 hour.
Pharmacodynamics - Nicotine is an agonist at nicotinic ACCh receptors.

- In the PNS, nicotine:
  - Causes adrenal medulla to release norepinephrine and epinephrine.
  - Sympathomimetic Effects
  - Activates receptors at the neuromuscular junction.
    - Muscle Tremor

In the CNS, nicotine activates presynaptic axo-axonic receptors.

![Diagram of axo-axonic receptors](image)

Increases NT release from Axon 1.
- Presynaptic Facilitation

Many different NTs can be facilitated.
- DA in the Nucleus Accumbens
- Catecholamines in brainstem arousal centers.
**Acute Toxicity**
- Nicotine is very toxic.
  - LD50 of ≈ 60 mg.
- Hard to fatally overdose.
  - Short half life.
  - Inefficient administration.
  - Area postrema “warns” the user.

**Chronic Toxicity**
- Nicotine *alone* isn’t associated with many serious illnesses...
  - … but nicotine isn’t the only substance in tobacco.
    - Carbon monoxide
    - “Tar” - Miscellaneous hydrocarbons.

**How dangerous are cigarettes?**
- Smoking accounts for 400,000 premature deaths in the U.S. every year.
  - 30% of all deaths due to cardiovascular disease.
  - 30% of all deaths due to cancer.
  - 80% of all deaths due to obstructive lung disease.
Cardiovascular Disease
- Smoking decreases the ability of the heart to get oxygen...
  - Carbon monoxide binds to blood hemoglobin.
  - Smoking is associated with atherosclerosis.
- … while at the same time making the heart work harder.
  - Sympathomimetic effects.

Lung Disease
- Tar accumulates in the lungs.
  - Emphysema - Damaged lung bronchioles cannot exchange gasses efficiently.

Cancer
- Tobacco contains carcinogens.
  - Example: Benzopyrene.

Tobacco use is associated with cancers of mouth, throat and literally every organ in the body.
- Sigmund Freud
Addiction
• Half of people who try cigarettes will become addicted
• Each day…
  ….6000 teenagers try their first cigarette.
  … 3000 will become addicted.
  … 1000 will die from smoking.
• 2/3 of smokers wish they could quit.
• Tougher to kick than heroin?

Why is nicotine so addictive?
• Nicotine gets into the brain very fast.
• Hundreds of “learning trials” each day.
• Smoking “conditioned” to certain situations.
  • Other smokers, alcohol consumption, meals, stress.
  • Stress increases nicotine clearance.

Physiological Dependence
• Withdrawal Symptoms:
  • Decrease in HR
  • EEG slowing
  • Irritability
  • Hunger
  • Headache
• Explanation of Nesbitt’s Paradox?
• Symptoms can be VERY long lasting
  • weeks or months.
Treatment of Nicotine Dependency

• 95% quit without formal help.
• Pharmacological treatment doubles success rate.
  • Nicotine Replacement Therapy
    • Skin Patch, Gum, Inhaler, Nose drops.

Antidepressant Therapy

• Smokers are more likely to be depressed.
• Nicotine can relieve depression.

• Antidepressants have been approved to treat nicotine addiction
  • Buproprion (Zyban)
    • DA reuptake inhibitor

Caffeine
Caffeine is the most widely used psychoactive drug in the world.

- Regularly consumed by 80% of U.S adults.
- Averaging 200-300 mg/day.
- Mostly coffee or tea.

- Categorized as a methylxanthine.

Products Containing Caffeine

- Coffee: ≈ 100 mg / 5 oz cup.
- Tea: ≈ 50 mg / 5 oz cup.
- Soft Drinks: ≈ 40 mg / 12 oz.
- Dark chocolate: ≈ 20 mg / oz.
- Milk chocolate: ≈ 6 mg / oz.

- Excedrin: 65 mg / dose.
- No-Doz: 100 mg / dose.

Psychological/Behavioral Effects

- Mild pleasure.
- Increase in mental alertness.
- Decrease of fatigue.
- Mild sympathomimetic effects.
- Vasoconstriction (less in heart, more in brain).
Very high doses (>500 mg) can lead to **caffeinism**.

- Anxiety
- Mild confusion
- Strong sympathetic arousal
- More common in people prone to anxiety disorders.
- Partly responsible for nicotine withdrawal?
- LD50 of ≈ 10000 mg.

**Pharmacokinetics**

- Easily absorbed orally.
- Metabolized by the liver.
- Half-life of ≈ 4 hours.
- Metabolizes twice as fast in smokers.

**Pharmacodynamics**

- Caffeine antagonizes adenosine at axo-axonic synapses.

- Adenosine is an inhibitory **neuromodulator**.
- Caffeine, therefore, facilitates NT release.
Caffeine…
- Facilitates DA release in cerebral cortex.
  - Rewarding effects.
- Doesn’t appear to affect DA release in nucleus accumbens.
  - Less addictive.
- Facilitates catecholamine release in:
  - PNS - sympathomimetic effects
  - CNS - arousal effects.

At high doses, Caffeine also antagonizes benzodiazepine receptors.
- Caffeinism anxiety.

Addiction and Dependence
- Low risk of psychological addiction.
  - But it does happen.
- Risk of physical addiction with high levels of use (≈ 500 mg/day).
  - Withdrawal symptoms.
    - Headaches
    - Fatigue
    - Diminished alertness
Cocaine and Amphetamine

Cocaine

- Natural Substance found in the coca leaf.
- Used first by South American Natives.
- Early medical uses:
  - Addiction
  - Depression
  - Hysteria
  - Mood Enhancement
- Sigmund Freud.
- Now used rarely medically (Schedule II Drug)

Amphetamine

- Ephedrine - Natural amphetamine no longer available as a supplement.
- Amphetamine is synthetic ephedrine.
- Methamphetamine - More lipid soluble form.
- Historic use similar to cocaine.
- Abused sources can be legally or illegally synthesized.
  - “speed”, “crystal”, “crank”, “ice”.
Effects of Cocaine/Amphetamine

- Euphoria
- CNS Arousal
- Insomnia
- Appetite Suppression
- Reversal of Fatigue
- Improvement of cognitive/physical performance.
  - Reverses at high levels.
  - Sympathomimetic effects

Cocaine has local anesthetic actions.

- Blocks voltage gated Na+ channels.
- Prevents transmission of pain/touch.
- Approved medical use.
- Not (usually) relevant to abuse.

- NOT an effect of amphetamine.

Drug forms

- As a salt: Cocaine HCl, Amphetamine sulfate, Methamphetamine HCl
- Dissolves easily allowing:
  - Nasal inhalation.
  - Poor absorption.
  - Injection.
  - Oral administration.
    - Basic pH gives poor absorption.
Drug Forms ctd...

- Cocaine is smokeable as a “Free Base”.
  - Free-base cocaine is explosive!
  - “Crack” cocaine and “Ice” are safer alternatives.

Metabolization and Elimination

- Cocaine
  - Mostly metabolized by liver.
  - Half-life ≈ 45 minutes.
- Amphetamine
  - Partly metabolized by the liver, but 40% excreted unchanged.
  - Half-life for amphetamine ≈ 8 hours.
  - Half-life for methamphetamine ≈ 5 hours.

Pharmacodynamic Effects

- Both drugs facilitate DA and NE transmission.
  - Cocaine blocks reuptake of DA and NE.
  - Amphetamine increases DA and NE release.
Pharmacodynamic Effects

- Facilitation of
  - DA in nucleus accumbens causes addiction.
  - NE in CNS causes arousal.
  - NE in PNS causes sympathomimetic effects.

Toxicity

- Acute Toxicity
  - Cardiovascular Problems
  - Epileptic Seizures
  - Coma and death
  - Rebound Depression

Acute toxicity continued…

Movement Disorders

- Abnormal repetitive movements
  - Repetitive Jaw Movements
  - Repetitive tasks.

- Likely due to effects on DA in movement centers of the brain.
  - E.g. Substantia Nigra
Acute toxicity continued…

**Toxic Paranoid Psychosis**
- Psychosis - “Loss of touch with reality”.
- “Amphetamine Psychosis”
- Symptoms:
  - Extreme Paranoia.
  - Hallucinations
    - Visual, Tactile (“cocaine bugs”)

**Chronic Toxicity**
- Nasal irritation.
- Malnutrition
- Sleep Disorders
- Neurotoxicity
- Major Depression
- Sensitization to psychosis induction.
  - Sometimes permanent?

**Dependence**
- High risk for psychological dependence.
- Lab animals will self-administer until death!
- Inhaled forms are most addictive.
Physical Dependence

- No obvious withdrawal symptoms.
- Some symptoms due to drug related lifestyle.
- Subtle signs after chronic or heavy use:
  - Depression
  - Fatigue
  - Hunger
  - Feeling “cranky”
- Can last for days or weeks.