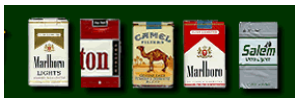


Psychostimulants

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.

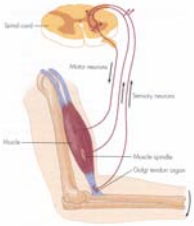
Nicotine easily crosses the blood brain barrier.

Metabolism

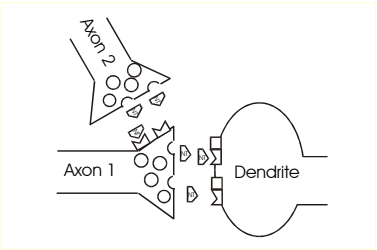
- 80-90% metabolized by the liver.
- Remainder secreted in urine.
- Half-life of ≈1 hour.

Pharmacodynamics - Nicotine is an agonist at *nicotinic* ACh 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.

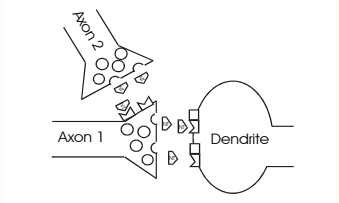


Increases NT release from Axon 1.

- 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

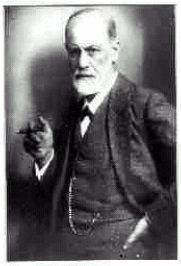
- Tar accumulates in the lungs.
  - Emphysema - Damaged lung bronchioles cannot exchange gasses efficiently.

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*.

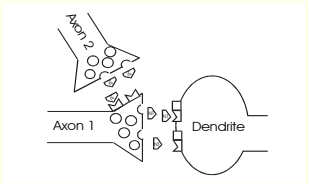
- Anxiety
- Mild confusion
- Strong sympathetic arousal
- More common in people prone to anxiety disorders.
- Partly responsible for nicotine withdrawal?
- LD50 of ≈ 10000 mg.

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...

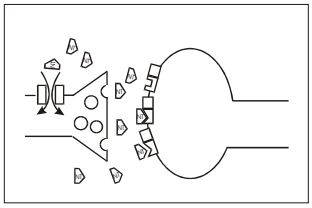
- Cocaine is smokeable as a "Free Base".
  - Free-base cocaine is explosive!
  - "Crack" cocaine and "Ice" are safer alternatives.

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

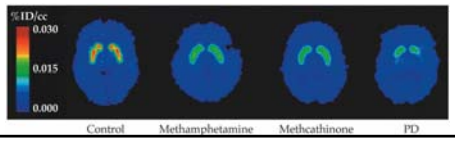
Acute toxicity continued…

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.