NICOTINE:
- Alkaloid in tobacco (~5% by weight): major psychoactive ingredient
- 1 cigarette ~ 9mg, but only 1mg absorbed

Routes:
Inhalation (smoking): fastest, 25% reaches brain within 7 sec via lungs)
Oral (chewing, moist snuff, gum): slowest, via oral membrane
Nasal (snuff): via membranes of nasal cavities

Absorption:
- Cigarettes: rapid, repeated administration

Metabolism and Excretion:
- Kidney and Liver, Milk
- Short half life (~ 2 hrs)
- Toxicity: ~60mg (1/2 cigar)

Peripheral Effects:
Sympathetic: STIMULANT
- Increased Heart Rate
- Increased Blood Pressure
- Secretion of NE and E from adrenals
- Vasoconstriction: narrowing of blood vessels

Parasympathetic:
- Increased Stomach Acid
- Increased Intestinal Motility

CNS Effects:
- Increased psychomotor performance
- Mild cognitive enhancements
- Reinforcement: readily self-administered

Mechanism of Action: Nicotinic Acetylcholine Receptor, nicotine = strong ligand

Acetylcholine (Ach): First transmitter identified (peripheral NS)
Distribution:
Diffuse reticular: lower hind brain near stem, involved in vigilance functions, wakefulness
Basal forebrain: projects to thalamus, hippocampus (learning), involved in memory and attention
-lesion here → amnesia, where cells die first from Alzheimer's
Intrinsic (basal ganglia, forebrain)

- Involved in muscle contractions
- Classical NT: choline and AcCoA from diet
- **Synthesis: Choline + Acetyl Coenzyme A –E→ Acetylcholine + Coenzyme A (Enzyme = Choline acetyltransferase**)

Acetylcholinesterase: enzyme that breaks down Ach into Choline and Acetate
Cholinesterase inhibitors used as pesticides

Acetylcholine Receptors:
- Ach Antagonists: Immobilize muscles by stopping muscle contractions, stops breathing

Muscarinic Ach Receptor: g protein coupled
- Agonist: Muscarine
- Antagonist: Atropine

Nicotinic Ach Receptor: ligand gated (Na+ let in)

- Agonist: Nicotine
- Antagonist: □-bungar toxin, curare (neurotoxins from snails/snakes)
- 5 Subunits: Pentameric structure
    - 2 □ subunits: where 2 molecules of Ach must bind to let in Na+ (EPSP-excitatory post synaptic potential)
    - Also □, □, □
- In brain: Nicotinic receptor = PRESYNAPTIC receptor, Ca^{2+} Channel

Actions on DA systems: Self-administration, addiction thru DA pathways
- Nicotinic receptors on DA terminals presynaptically opens Ca^{2+} channels → increases DA release
- Caudate: involved in movement
- Nucleus Accumbens: addiction center
- 6-OHDA lesion (loss DA neurons) DECREASES Nicotine self-administration
-VTA: put Nicotine in VTA → changes in locomotor activity
- Put DA antagonist in Accumbens → blocks nicotine's effects

SEDATIVE HYPNOTICS
- Depress CNS and behavior
- All LETHAL at hight doses, except anxiolytics
    Alcohol
    Barbiturates: Strongest ~ general anesthetics
    Non-Barbiturate Hypnotics
    Anxiolytics: weaker sedatives, for anxiety and sleep- work thru same mechanism

Continuum of Behavioral Sedation:
Normal→ Anxiety relief → Disinhibition→ Sedation→ Hypnosis (Sleep)→ General Anesthesia→ Coma→ Death

Addititve Effects: mixing sedative hypnotics → super additive effect
    - ex: Alcohol + Valium (anxiolytic) → huge effect, larger than sum of both

Cross Tolerance: Tolerance to one group leads to tolerance to others
    - ex: Alcoholics (high Alcohol tolerance) need MORE anesthesia to be put under

Alcohol = ethyl alcohol = ethanol (grain alcohol) = EtOH
- NO accepted medical use except aseptic (kills bacteria, but not very effective)
- Affects blood pressure (can increase or decrease, especially in extremities)
- Inhibits ADH (ant-diuretic hormone) → dehydration from constant urination

Others: Isopropyl (rubbing alcohol), methyl alcohol = methanol (wood alcohol, MeOH), both are toxic

Absorption:
- Oral administration
- Most absorbed in Small Intestine
- Drinking without food in stomach increases BAC
- Easily distributes throughout body

Elimination:
- ~10% excreted unchanged thru sweat, tears, urine, breath

Metabolism:
- Mostly metabolized in LIVER by enzyme Alcohol Dehydrogenase
- EtOH → Acetaldehyde (TOXIC when builds up in liver) → $H_2O + CO_2$
    - Enzyme = rate limited, can only metabolize ~ 6-8g/hr
- MeOH → Formaldehyde + Formic Acid (TOXIC)
- Tylenol (acetaminophen) causes Acetaldehyde to build up, can be TOXIC if taken with alcohol

Microsomal Ethanol Oxidizing System
- only 5-10% of metabolism
- But with chronic consumption (alcoholics), system upregulated and increases to 50-60%

→ Tolerance b/c system immediately metabolizes alcohol before reaches brain
→ Damage from alcoholism: IRREVERSIBLE MEOS = liver enlargement
- Role in cross-tolerance to barbiturates

Effects on Behavior/Physiology
- Impairs Sensory Motor Functions
  - Direct correlation between BAC and motor coordination
  - Legal limit = 0.08 (80mg/100mL)
- Effects on Cognition and Affect (if BAC = 0.10 equals 100mg/100mL)
  100-150mg/100mL → Disinhibition
  150-300 → Sedative Effects
  300 → Stupor
  400 → Lethal dose, Respiratory Depression

Tolerance: Alcohol shows acute tolerance (right away)
  Ex: BAC when "sober" after continuous drinking is higher than "intoxicated" BAC
- Chronic Tolerance: Dose effect curve shifts Right (need more to get same intoxication)

Withdrawal:
- Can be very severe, even lethal: very dangerous for all Sedative Hypnotics (except anxiolytics)
- Delirium Tremens ~ seizures, epilepsy
  - Way for brain to excite itself back to normal after long depression
-Brain Damage: Korsakoff's syndrome ~ amnesia
- Physiologically: convolutions in brain are more spaced out, larger ventricles

Mechanisms of Action:
- Increases fluidity of plasma membrane → more things can cross
* Effects on membrane-bound proteins:
  $GABA_A$ Receptor: Alcohol = AGONIST here, causes sedative effects
  NMDA receptor: Alcohol = ANTAGONIST → fetal alcohol syndrome
- Reduces Ca2+ neurotransmission

Fetal Alcohol Syndrome: includes all sedative hypnotics (readily cross placental barrier)
- Mild-severe retardation, neurobehavioral problems
- Mechanism: Blockade of NMDA receptors → apoptosis (~cell suicide), brain degeneration
  *Alcohol = NMDA receptor ANTAGONIST
- Apoptotic Neurodegeneration: unique to alcohol, barbiturates, and benzodiazepines (act at $GABA_A$ receptors)
  - Alcohol effects may be due to combination of NMDA and $GABA_A$ receptor actions

<u>BARBITURATES</u> ~ sleeping pills, tranquilizers, "downers"

History:
- Barbituric Acid (1864): surgical sedative
- Barbital (1903)
- Phenobarbital (1912): sleeping pill

Classes:
Long Acting: Phenobarbital (Luminal) ~ 8-12hrs, surgery
Intermediate: Pentobarbital (Nembutal) ~ 2-8hrs
Short: Secobarbital (Seconal) ~ 1-4 hrs
Ultra-Short: Thiopental (Pentothal, truth serum b/c uninhibited) ~ 5-30 min

Medical Uses:
- Sleep Induction: not used anymore
  - not good quality sleep, very deep but no REM
  - stop barbiturates → REM rebound
-Anticonvulsants
-General Anesthetics: not that safe
- Sedatives
- Alcohol Withdrawal

- Anti anxiety (historical use, not anymore)

Illicit Use:

- Used for effects similar to alcohol
- Combined with other drugs (ie stimulants or opiates to even out side effects)

*Shows Very Rapid Tolerance: cross tolerance with alcohol (MEOS)

- Severe withdrawal: Life Threatening
    - Grand mal seizures
- Respiratory Depression: easy to OD
- Used in 50% drug-related suicides

ANXIOLYTICS: safer than barbiturates (which cause too much dependence and death)

Meprobamate (Miltown) ~ still causes dependence

Benzodiazepines (BZ): many on market, differences in duration

- Cant OD on BZs

Chlordiazepoxide (Librium)
Diazepam (Valium) – longest acting
Oxazepam (Sevax)
Nitrazepam (Moyodon)
Flurazepam (Dalmane)

Second Generation Anxiolytics: not sedative hypnotics, less sedation

- Busipirone
- Serotonergic Actions (SSRI's)

Medical Uses: ALL produce amnesia to some degree

- Pathological Anxiety: most prescribed use
- Severe emotional distress
- Relief from agitation and Alcohol withdrawal
- Sedation (sleep-inducing)
- Presurgery Sedation

ex: Versed: IV, short acting, fast, marked amnesia

Tolerance:

- As tolerance builds with repeated use, margin of safety NARROWS: ED approaches LD

Therapeutic Effects:

- Calm, Relaxation
- Side effects:

Motor incoordination
Intoxication at high doses (like alcohol)
Memory loss
Deep sleep and coma at high doses
Respiratory Depression: NOT lethal at high doses, but can potential other drugs effecs (alcohol)

Abuse:

- Not self-administered, low preference
- Date Rape:

Rohypnol (flunitrazepam, a BZ): like Valium, but more potent and long lasting, produces a lot of amnesia
Micky Finn (chloryl hydrate): ~ anesthetic
GBH/GHB (□-hydroxybutyric acid): like GABA

Mechanisms of Action

Early studies: potentiates GABA effects (inhibitory transmitter)

Discovery of BZ binding sites: cortex, hippocampus, amygdula

- GABA receptor = big complex with multiple active sites, has BZ site
- Correlation between anxiolytic effect and GABA binding

GABA Neurotransmission
- Traditional NT, single step synthesis from GLUTAMATE (amino acid, excitatory NT- opposite effects)
- Distributed throughout CNS, local and projection neurons
- GABA: ubiquitous INHIBITORY NT → sedating effects, can displace BZ
→ HYPERPOLARIZES neurons, halts action potential

GABA Receptors:

$GABA_A$: Ionotropic – lets Cl- thru (inhibitory)→ hyperpolarization
- part of large complex, forms Chloride channel
- GABA INCREASES Cl- conductance

AGONIST: Muscimol – poison, shuts everything down

ANTAGONIST: Bicuculline: massive and rapid depolarization →seizures

INVERSE AGONIST: produces OPPOSITE effects of Agonist
- □-Carbolines: Decrease frequency of openings →panic, anxiety
- Negatively regulate receptor

* Major site of Sedative Hypnotic Action
- GABA, BZ and Barbiturates act on different sites on this receptor
- BZ/BARB modulate what GABA does, no direct action alone, needs GABA to bind also
- BZ/BARB potentiate Cl- influx produced by GABA→ bigger inhibition
- Some endogenous ligands at BZ site →anti-anxiety

$GABA_B$: Metabotropic, g-protein coupled

Different Mechanism:
- Barbiturates: Increase long duration open states, more Cl- influx, unsafe
- Benzodiazepines: Increase Frequency of openings, safer
- Positively modulate $GABA_A$ receptor

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Marijuana & Cannabinoids
- Cannabis sativa, hemp: one of the earliest non-food plants cultivated
- Cannabinoids: pharmacologically active compounds, there are over 60 cannabinoids- focus on Δ9-THC
- Marijuana is mixture of leaves, stems and tops; 1-3% THC content in 60's, 8-10% THC content in 90's (marijuana got stronger over the years)
- Hashish: dried resin from top of female plant; THC content usually 2-5% but up to 15%
- Hashish oil: organic extraction from hashish; THC usually 10-20% but up to 70%
- Synthetic cannabinoids are developed for research, some of them are very potent (Marinol)

□ Pharmacokinetics: absorption, metabolism and clearance
- Very lipid soluble, good absorption with rapid peak if smoked (20-37%); absorption is slower with oral administration
- Metabolism rapidly drops initially due to redistribution to fats; slower metabolism in liver; metabolites may persist for a week
- ℘ *Metabolites may be the major biological active compound* : primary metabolic product of Δ9-THC is more potent than Δ9-THC/ there is a delay between peak plasma level and reported "high"

□ Effects: marijuana is not lethal even at very high doses
- Low to moderate doses: disinhibition, relaxation, drowsiness, feeling of wellbeing, euphoria, sensory-perceptual changes, recent memory impairment, and psychomotor function impaired
- High doses: pseudohallucination, synesthesias, impaired judgment and reaction time, pronounced motor impairment, disorganized thoughts, confusion, paranoia, agitation
- Amotivational syndrome with repeated use
- Potential medical uses include: glaucoma, antiemetic, anticonvulsant, appetite enhancer, analgesic

□ Mechanism of action
- Nonspecific actions include change in membrane fluidity

- Specific actions: presence of cannabinoid receptor is likely due to- effectiveness of small dose, different effects of d and l isomers, marked structure-function effects, and inhibition of cAMP formation via G protein
- Development of synthetic cannabinoid receptor is difficult b/c Δ9-THC binds weakly and is not a full agonist
- Cannabinoid receptors are conserved across mammalian species; its distribution is similar to cAMP distribution; both CB-1 and CB-2 (periphery) receptors are G protein-coupled; cannabinoid receptor density is very high, as it can be compared to amino acid receptors

 Pharmacodynamics

- Release increases Ca++
- CB-1 receptors are presynaptically located
- Retrograde signal: signal goes from post-synaptic to pre-synaptic
- Cannabinoid release inhibits GABA release

 Endogenous Cannabinoids

- Anandamide ("bliss" in Sanskrit) is derived from arachidonic acid
- Anandamide has similar actions to cannabinoids: inhibits of cAMP via cannabinoid receptor, inhibits of cannabinoids binding, partial agonist at CB-1, decreases motor activity, has antinociceptive effects
- 2- arachidonyl glycerol is a full agonist at CB-1 in brain in higher concentration than anandamide

 Locus of actions: relationship between action and sites of action is not known

- Speculation: memory effects- hippocampus
  reward- mesostriatal DA system
  motor activity- basal ganglia, cerebellum
  analgesic effects- spinal cord and peripheral tissue
- THC increases % change in accumbens dopamine level

PCP

▪ Phencyclidine (PCP): street names include PCP, angel dust, crystal, horse tranquilizer

- Dissociative anesthetic produced as an animal tranquilizer;related to Ketamine, a veterinary medicine with better safety margin than barbiturates- used in emergency surgery in human
- Illicit use was widespread from late 70's to early 80's; only few people were habitual users
- One of the cheapest drugs because of its synthetic nature
- Sometimes PCP is added to low-quality marijuana to increase the efficacy "sherm" or "embalming fluid" on cigarettes or marijuana
- Taken orally, intranasal, I.V., or smoke

 Effects of PCP

- Low dose (1-5mg): produces alcohol-like effect
- Moderate dose (5-10mg): distortion of space and time, psychotic reactions, anesthesia and analgesia, blank stare, amnesia, mutism
- High dose (>10mg): model of acute schizophrenia, including true hallucination (=open-eyed hallucination; user does not realize hallucination is unreal and may attempt to dangerous things), sometimes violent and abusive behavior
- Overdose: respiratory depression/ seizures; low safety margin

 Self-administration

- Readily self-administered in animals; exhibits modest tolerance

 Mechanism of action: VERY DIRTY; has many effects

- PCP binds at sigma site and PCP site on NMDA glutamate receptor; binding at sigma site generalizes with benzomorphan, opium that is not addictive but still produces analgesia and hallucination

 Glutamate: principal excitatory NT in brain; depolarizes virtually all cells

- Glutamate receptor types include ionotropic subtypes (AMPA, Kainate and NMDA) and metabotropic mGlu receptor; NMDA receptor is usually blocked off by Mg^{++}, opens only when there is a large postsynaptic depolarization and glutamate present; opening of NMDA receptor allows Na^{+} and Ca^{++} influx
- PCP is a noncompetitive antagonist at NMDA receptor; PCP site is inside the channel- PCP binding blocks the ion flow-> NMDA receptor stops working; PCP does not affect AMPA or Kainate receptors
- PCP enhances DA release- addiction potential

 Neuropathology

- Multiple vacuoles (holes) form in cytoplasm of some neurons and mitochondria disappear 2-4 hrs after treatment; this may be causing toxic psychosis since nerves cannot function normally with vacuoles; although there is no known significance of vacuole effects on neuron, it couldn't be good to have holes in your neurons
- Vacuoles disappear within 24 hours
- Sustained activation of NMDA receptors at critical stages in development activates programmed cell death-this can lead to fetal alcohol syndrome; we see this effect with PCP, Ketamine, and ethanol

 Glutamate excitotoxicity

- Neurons, when overactivated, can die- hypoxia (drop in blood oxygen level) is one cause of neural excitotoxity, brain starts to wake itself up by releasing increased amounts of glutamate leading to increased amounts of Na^{+} and Ca^{++} influx
- MK-801 (NMDA receptor antagonist), if given during stroke attack, will block off Ca^{++} influx and prevent further cell death; need to control side effects (i.e. hallucination) in order to be approved (not likely)

Hallucinogens

 Common features

- Hallucinogens have the ability to evoke hallucinations, pseudohallucinations (closed- eye hallucination where the user is aware that hallucination is unreal) and illusions
- Psychomimetic: the ability to mimic endogenous psychosis; schizophrenia-like symptoms
- Phantasicum, Psychedelic: "mind-expanding"; change in perception of reality

 Classes

1. The LSD "family"
- Indole type halluninogens, structurally similar to 5-HT
- LSD (lysergic acid diethylamide)

2. The Phenylethylamines
- Structurally similar to catecholamines, has mixed hallucinogenic and stimulant effects
- mescaline (active ingredient in peyote), methoxyamphetamines (synthetic derivatives of mescaline)

 LSD: one of the most potent drugs

- First synthesized by Hofman in 1938 from ergot; Hofman wrote a vivid, accurate account on LSD
- LSD is absorbed rapidly, takes 1/2- 1hour to work; tolerance is relatively short; 24 hours
- Major effects include sensory-perceptual, psychic experiences, and somatic effects
- Adverse effects include bad trips and flashbacks (these tend to run in family; some people are more prone to have bad trips and flashbacks)

 LSD type hallucinogens- none of these are addictive

- Psilocybin and Psilocin is active ingredient in "magic mushroom"
- Much weaker version of LSD; similar comparison between cocaine vs. amphetamine
- DMT (Dimethyltryptamine): naturally occurring, not orally active, short duration of action
- Morning glory seeds: contains LSA (lysergic acid amide)
- Bufotenin (5-hydroxy-DMT): toad licking
- Harmine and Harmaline

 The Phenylethylamines

- Mescaline (schedule I) is found in peyote cactus; little weaker than "magic mushrooms" but mixed hallucinogenic and stimulant effects; mescal button is a little piece of cactus that has the active ingredient
- Methoxyamphetamine is synthetic derivatives of mescaline; many of these are called "designer drugs"

DOM (dimethoxymethylamphetamine) is called STP, for serenity, tranquility, peace
TMA (trimethoxyamphetamie) is similar to mescaline, but more potent
MDA and MDMA (known as extacy)

- With phenylethylamines, continuum between amphetamine like effects and LSD like effects exist; binding toward DA induces stimulant like effect, while binding toward 5-HT induces hallucinogen like effects

 Hallucinogen mechanism of action

- Only short-term tolerance (~24hrs) to LSD, no withdrawal, dependence or addiction; reason LSD being a schedule I drug is not its addictive properties (LSD is not addictive), but we don't want people driving around on LSD
- LSD is not lethal at very high doses
- LSD produces cross tolerance for hallucinogenic effect
- Current hypothesis: ℘ *LSD and other hallucinogens are 5-HT_{2A} postsynaptic receptor agonists!*