

Barbiturates

- Bayer in 1864 combined urea (urine) and malonic acid (apples)
 - barbituric acid
- Origin of the name
 - Barbara contributed the urine
 - Barbara was a barmaid where he went to celebrate
 - St. Barbara - patron saint of artillery

Barbiturates

- 1903 - **Veronal** (after Verona, e.g. Romeo & Juliet- added "al" to end)
- New barbiturates synthesized rapidly in early 1900's
- 2500 synthesized, about half dozen served all clinical applications
- Use increased until 1960's

Barbiturates

- Pharmacodynamics
 - Classified by duration of action
 - determines use
 - anesthesia – short acting
 - sleep induction - medium
 - anticonvulsant - long as safely possible
- Administered orally most often
 - exceptions - i.v. for convulsant emergencies
 - anesthetic action & drug abusers

Barbiturates

- Barb's depress all excitable nervous tissue
 - CNS most sensitive
- Mechanism thought to be at GABA synapse
 - Low doses - increase receptor sensitivity to GABA to potentiate and prolong its effects
 - Higher dose mimic GABA inhibition possibly by directly activating chloride channels

■ The GABA Receptor

- Excitation produces an influx of chloride (Cl⁻) ions, which hyperpolarizes the neuron

■ The GABA_A Receptor Has Two Sites:

- Sedative-Hypnotic Site: Alcohol and barbiturates
 - Directly influences Cl⁻ influx
- Antianxiety Site: Benzodiazepines
 - Enhances binding effects of GABA
 - Effect is dependent upon amount of GABA present
 - Harder to overdose

Alcohol or barbiturate
Sedative-hypnotic site
GABA
Chloride channel
Cl⁻

Benzodiazepine
GABA
Antianxiety site

Binding of sedative-hypnotic drugs (such as alcohol or barbiturates) acts like GABA, causing increased chloride conductance.

Binding of antianxiety drugs (benzodiazepines) enhances binding effects of GABA.

Because of their different actions, these drugs should never be taken together. Combined doses can cause coma or death.

■ Allopregnanolone

- Natural hormone produced by pineal gland
- May bind to the sedative-hypnotic site of the GABA_A receptor
- Higher levels in women than in men

■ Fetal Alcohol Syndrome

- Pattern of physical malformation and mental retardation observed in some children born to alcoholic mothers

Barbiturates

- Behavioral effects very similar to alcohol
 - disinhibition, euphoria, sedation, loss of motor control
 - sleep, anesthesia & death
 - also tolerance, physical dependence, & similar withdrawal
- BIG TIME OD Potential

Barbiturates

- CNS regions affected by Barbs same as alcohol
- Low Dose
 - Reticular activating system depression
 - Septal projections to amygdala = Anxiolysis
- Higher Dose
 - Global depression of neural activity
 - Final symptoms respiratory depression and spasm of larynx

Barbiturates

- Medical uses for barbs were anxiety, insomnia, and epilepsy
 - most uses replaced by benzodiazepines except epilepsy
 - Phenobarbital most commonly prescribed anti-epileptic
 - cheap, low in toxicity, effective dose well below hypnotic level
 - Side effects all similar to alcohol
 - Used today for general anesthesia

Barbiturates

- Most commonly abused are short acting Seconal (reds)
 - Preferred means for suicide
 - Most common barbiturate fatality results from combo of alcohol and barbiturates
 - Half LD50 of seconal with quarter LD50 of alcohol will kill

Benzodiazepines

- Because barbiturates cause problems similar to those caused by alcohol
 1. suppresses respiration & can lead to death
 2. not overly safe
 3. high dependence potential
 4. easily abused
 5. act synergistically with alcohol to induce death
- Then we need a better drug --- Benzos

Sedatives: Benzodiazepines

- Mid 1950's known as "anxious age"-many drugs developed
 - 3 main classes
 - Anti-psychotics
 - anti-depressants
 - Miltown
- Late 1950's accidental discovery of drug with sedative, anti-convulsant and muscle relaxant properties
 - Very low toxicity

Benzodiazepines

- Drug named Librium & released in 1960
- Within 3 months #1 prescribed sedative
- Valium, more potent than librium, introduced 3 yrs later
 - From latin vale - to be strong or well (diazepam)
 - Went on to become most prescribed drug of any kind
 - Replaced barbs as hypnotics (sleeping pills) in 1970's with introduction of Dalmane

Benzodiazepines

- Went on to sell like hotcakes - 1975 104.5 million prescriptions
- 1977 decreased to 54 mill but 8000 tons still consumed that year
- that's 2,415,000 individuals at 2-3 doses per day
- Common description of user
 - middle age to elderly
 - residing in Western U.S.
 - female

Benzodiazepines

■ Benzodiazepines

- | | |
|-------------|------------------|
| 1. Librium | Chlordiazepoxide |
| 2. Valium | Diazepam |
| 3. Dalmane | Flurazepam |
| 4. Xanax | Alprazolam |
| 5. Halcion | Triazolam |
| 6. Clonopin | Clonazepam |

■ Primary Uses (based upon duration of action)

- 1) Muscle Relaxant
- 2) Sleeping aids
 - favorites are triazolam and flurazepam
- 3) Anxiety (Generalized anxiety disorder)
- 4) Epilepsy - Clonazepam (Clonopin)-
- 5) Panic attacks - Xanax (alprazolam)
 - anti-depressant action in some situations

Benzodiazepines

■ Pharmacokinetics

■ Administration

- most taken orally - completely absorbed via G.I. Tract. Absorbed slowly
- Can be given by IV (seizure or pre-surgery)

Benzodiazepines

■ Agonist at GABA receptor

- benzodiazepine site present at GABA receptor
- GABA tightly coupled to Cl⁻ channel (opens Cl⁻ channel)
- get full effect if both GABA and benzodiazepines are present
- Cl⁻ enters cell which inhibits firing

Benzodiazepines

- Benzodiazepines have active metabolites via biotransformation
- Breakdown by liver
- Tolerance does not appear to develop for anxiolytic action
- Does fairly rapidly for effects on sleep

Benzodiazepines

- Location of binding sites
 - Primary sites
 - cortex
 - limbic system
 - Secondary sites
 - thalamus
 - cerebellum
 - locus coeruleus

Benzodiazepines

- Actions
 - anticonvulsant cortex
 - hypnotic cortex and locus coeruleus
 - anxiolytic limbic system and locus coeruleus

Benzodiazepines

- Problems with benzodiazepines
 - over prescribed
 - often given on request from patient
 - treat the anxiety but not the source of problem
 - memory impairments
 - especially when used as hypnotic agent-have amnesia for events while individual is receiving the drug
 - can provide a sense of euphoria
 - abused in combination w/alcohol for greater sense of euphoria
 - ataxia-incordination
- Benzodiazepines have a fairly safe therapeutic index
- Rohypnol – Powerful benzo that is an amnestic. One of the unfortunately many date rape drugs.

Inhalants

- Adhesives - Glue
- Aerosols – Spray paint
- Anesthetics - NO
- Cleaning Agents – Degreaser
- Solvents - Nail polish remover, gas
- Gases - Butane
- Nitrites - Poppers

Inhalants

- Not all are true depressants
- NO is a true depressant
- Most produce a dizzy “euphoric” rush
- Effects are complex and not well understood

Inhalants

- Abused by children and adolescents
- Certain subcultures as well
 - Popper and gay men
- A particular problem in homeless and runaway populations

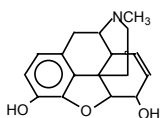
Opiates

- Opiates are natural and synthetic compounds that come from or are copied from OPIUM – The resin of the opium poppy
- Natural Narcotics
 - Opium
 - Extracts – Morphine & Codeine
- Semisynthetic Narcotics
 - Slight changes to chemical composition of morphine
 - Heroin
- Synthetic Narcotics - Produce opiate like responses
 - Methadone, Talwin, Darvon, Demeral
 - BUPRENORPHINE – Partial agonist

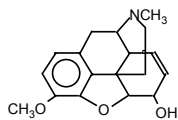
Definitions

- Opioid - generic term for class
- Opiate - drug from opium alkaloids
- Opium - Gk. - *juice*, dried residue from seed capsules of *Papaver somniferum*
- Narcotic - legal term
- Analgesia - absence of pain
- Anesthesia - absence of sensation

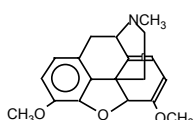
Opium Alkaloids (*Papaver somniferum*)



morphine

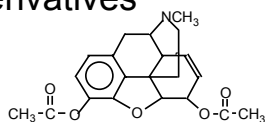


codeine

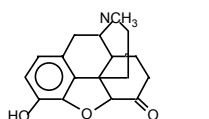


thebaine

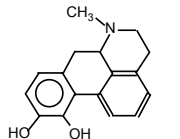
Semi-Synthetic Derivatives



heroin

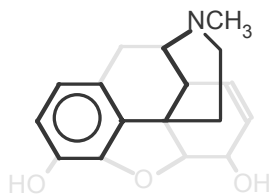


hydromorphone
Dilaudid®



apomorphine
emetic

Structure-Activity Relationships



morphine

phenyl-N-methyl piperadine =
agonist

Opiates in US Early 1900's

- Harrison Act of 1914
- No ban on opiates, but doctors had to register with IRS
 - Decreased prescriptions
- Users not seen as victims but weak-willed
- Heroin drug of choice in black market
 - Shift of users from women to white urban adult males

Opiates Use in 1980 -Today

- Fentanyl "China White"
 - Surgical anesthetic & prescription painkiller
 - 10 to 10,000 X stronger than heroin
 - Growing illegal market = growing deaths
- Heroin – Schedule I
- Morphine Schedule II
- Vast majority of therapeutic opiates are synthetic
- Huge illegal market and trade w/large dependence problem in US and abroad

The Production of Opiates

- Opium grown in 2 primary regions of world using simple farming techniques
- Poppies grown, petals fall, small incisions, liquid oozes out = opium
- Opium - 10% morphine 0.5% codeine
- Morphine refined in growing areas then transported or processed
 - Heroin – Simple process to create
 - Diluted to 1-10% and distributed

Absorption, Distribution, Metabolism & Excretion

- Most opiates poorly absorbed through GI tract (except codeine)
 - Effective nasally and through lungs
 - Opium frequently smoked, heroin snorted
 - Most effective i.v. (heroin 100 times more potent i.v. than orally)

Absorption, Distribution & Excretion

- In bloodstream distributed throughout body
 - accumulating in kidney, lung, liver, spleen, muscle & brain
- Opiates and blood brain barrier
 - Morphine does not cross BBB well
 - only 20% of circulating enters brain
 - 30-60 min to reach significant brain concentrations

Absorption, Distribution & Excretion

- Heroin more lipid soluble so penetrates BBB better
 - Heroin converted to morphine once it cross the BBB
- All have somewhat different pharmacological effects
 - Differ in potency, duration of action & oral effectiveness
 - Heroin more potent than morphine when injected, but same when taken orally.

Medical Use

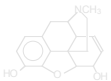
- Analgesia
- Sedation-markedly differs between individuals
 - poor sedative in general
- Anti-diarrhea agents
 - extremely effective for dysentery (1800's)
 - were the only effective agents in that time

Mechanism of Action

- Act via the endogenous opiate system
 - 1960's discovery of the opiate antagonist naloxone
 - Implication of common receptor site for opiates actions
- 1973 discovery of "opiate receptors" in brain
- Led to discovery of several "endogenous opiates" in 1975
 - Endorphin
 - Enkephalin
 - Dynorphin

Opioid Receptors and Ligands

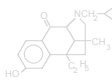
Mu (μ)



morphine
 β -endorphin

analgesia (μ_1)
euphoria
 ∇ respiration (μ_2)
dependence

Kappa (κ)



ethyl
ketocyclazocine
dynorphin

spinal
analgesia
sedation
no respiratory
depression

Delta (δ)

Tyr-Gly-Gly-
Phe-Leu

leu-enkephalin

neuromodulation
neuroendocrine
low addiction

Pharmacological Actions

- Primary sites of action - **CNS and GI tract**
 - Abuse of opiate use due to
 - **Analgesia** (best for dull continuous, not sharp)
 - Due to CNS not PNS effects
 - **Euphoria** (dream like state with intense visions)
 - Relives negative mood states

Side Effects

- Vomiting
 - very common with first dose
- Respiratory depression
 - Decrease sensitivity to CO₂
 - Occurs at low doses-those common for analgesia
 - Increase dose-increase depression
 - Most common cause of death in overdose

Side Effects

- Body temperature
- Resetting of body temperature thermostat
 - with limited use-lowers temperature by about 1 degree
 - can persist for a months
- Sex hormones
- Inhibited
 - males-decreased testosterone levels-decreased sex drive
 - Females-decreased estrogen

Side Effects

- Cardiovascular effects
 - increased skin blood flow-gives them a warm feeling
 - Blood pressure decrease upon standing -faint
- Pinpoint pupils
 - Signs of overdose
 - Seizures

Tolerance & Dependence

- Develops fast with repeated use
- More rapidly and to greater degree as potency increases
- Heroin & methadone develop different patterns for withdrawal
 - Heroin withdrawal begins 4-5 hrs after last dose
 - strong flu like symptoms
 - greatest magnitude of symptoms between 24-72 hrs
 - pretty much done in a couple of weeks

Tolerance & Dependence

- Methadone withdrawal 24-48 hrs after last dose
 - withdrawal symptoms reported to be less intense
 - however, much greater duration
 - can take months to clear all withdrawal symptoms
- Methadone used as a replacement for heroin and other opiates in dependent individuals
 - Longer half-life
 - Slower less intense effects – no euphoria
 - Can be taken orally – no needles
 - Cheap
 - Blocks heroin effect

POSSIBLE ROLES

- Memory
- Learning
- Stress response
- Reproduction
- Appetite
- Temperature regulation
- Acupuncture
- Shock

Endorphins

“endogenous morphine-like”

- Found in pituitary and hypothalamus
- β -endorphin most abundant
- Linked to ACTH biosynthesis

MECHANISMS OF ACTION

- G-proteins
 - Synaptic Neuromodulation
- Inhibit Neurotransmitter Release
 - (ACh, NEP, DA, 5-HT, substance P)

Hallucinogens

- Called by many different names
 - Psychotogens
 - Psychotomimetics
 - Psychedelics
- Primary effect is to produce perceptual changes & hallucinations
- Can influence several sensory systems perception of time, space & events

What are Hallucinations?

- True Hallucinations
 - Sensory experience in the absence of stimulation
 - Schizophrenia, can't tell that it's not reality
- Most hallucinations actually produce illusions
 - Distortion of real stimuli (tracing, colors ...)
 - person knows effects are due to drug
- Western societies consider hallucinations an abnormal state
 - In other societies they are viewed as valuable
 - Provide insight and/or are of religious significance

Different Types of Hallucinogens

- Serotonergic
 - LSD
 - Psilocybin (mushrooms)
 - Psilocin
 - Mescaline
 - MDMA (ecstasy)
- Cholinergic
 - Muscarine
 - PCP (Phencyclidine)

LYSERGIC ACID DIETHYLAMIDE (LSD)

- Lysergic acid – Derived from ergot alkaloids
- Ergot is a poisonous fungus that infects rye & other grains & grasses
- Albert Hoffman 1938 synthesized #25 in series of new molecules doing ergot alkaloid chemistry
- 1943 returned to #25 making new batch & absorbed some through skin

LSD in the USA

In the 1950s:

- Clinical usage: Supplied to psychologists & psychiatrists
- Military Usage: U.S. military & CIA as incapacitating agent & truth drug
- US government gave LSD to unsuspecting individuals to study effects

LSD in the USA

- 1960's popular use advocates
 - East Coast - Timothy Leary (clinical psychologist at Harvard)
 - West Coast - Ken Kesey (noted author)
 - graduate student in California administered to in psychology study
 - shortly after this goes to work in psychiatry
 - year later writes One Flew over the Cuckoo's Nest

LSD in the USA

- Spread through country with huge publicity until peak 1968 to 1972
- Schedule I in 1968
- Stuffy politicians didn't know what to do because LSD was used by white, middle to upper class, college students
- Early 1990's LSD came back

Pharmacology of LSD

Pharmacological Effects

- Effects heavily dependent on dose taken
 - not just intensity of effects but type of effects
- Low doses = mild perceptual alterations
 - comparable to effects of marijuana use but greater clarity

LSD & Neurotransmission

- Binds to 5-HT₂ receptors
 - agonist effect
- Increases amount of sensory information getting to cortex
 - This is how the drug influences perception especially for vision

Effects of LSD

High Doses

- Progression through mental & emotional experiences
- 6-12 hrs duration
- Each trip unique, highly dependent upon setting & personal expectations
- Can alter subjects emotional feelings during trip by experimenters previous behavior
 - warm & supportive or suspicious & non-supportive

Effects of LSD

Effects of drug come on in about 30 min

- first signs are autonomic activation
- followed by overt behavioral signs - loosening of emotional inhibitions
 - giddiness, laughter for no reason
 - mood euphoric & expansive but labile mood swings notable
- abnormal color sensations, luminescence
- colors reported as more brilliant

Effects of LSD

- Space & time disorders
- Added depth with loss of perspective - up/down altered
- Close in space influenced more than distant
- General slowing of time reported

LSD Hallucinations

- Gratings, latticework, honeycomb, chessboard, tunnels, funnels alleys, cones, vessels, & spirals
 - can be present with eyes open or closed
- Involves bright light in center with figures moving in from periphery
- Forms appear to move in depth & take on color shades, red common
- Sounds can take on visual forms
 - Music may take on enhanced meaning or intensity
 - Synesthesia

LSD & Bad Trips

- Psychological impact traumatizing, imagery is dark, insights appalling
- Usually occur in novice users, feel out of control
- Generally negative set & setting are key contributing factors
- Can lead to suicide or prolonged psychotic reaction
- Can usually be talked down from a bad trip

LSD & Flashbacks

- Spontaneous recurrence of trip after period of normalcy
- Can occur after long periods of abstinence
- More common after multiple high dose use
- Prolonged afterimages for days & weeks after
 - tripping mechanism unknown
- Can be brought on by other drugs or setting
- Most commonly reported in lowlight situations
- Not intrinsically dangerous & usually go away
- Strychnine

Psilocybin/Psilocin

- Magic Mushrooms, Liberty Caps
 - Central America & northwestern US
 - Last about 6 hours
 - Need a lot to get same effect as LSD
 - Weak 5-HT hallucinogens
 - Also found in nutmeg & mace
 - Same basic effects as LSD
 - Mushrooms occasionally toxic

Ecstasy

- MDMA
- Synthesized in 1912
- Structurally related to amphetamines
 - Designer drug
 - Weak in altering perceptual functions
 - But strong effects on emotions - empathogen
 - Used in combo with psychotherapy

Ecstasy Effects

- Stimulant effects typically noted shortly after ingestion
 - increased heart rate
 - increased blood pressure
 - dry mouth
 - decreased appetite
 - increased alertness
 - elevated mood
 - jaw clenching

Ecstasy Effects

- Subjective Effects
 - Euphoria
 - Increased physical and emotional energy
 - Heightened sensual awareness
 - Subjective feeling of increased closeness or enhanced communication

Ecstasy Toxicity

- Difficult to judge given poor quality of most ecstasy.
 - What most people take is full of nasty things
- Pure MDMA leads to destruction of serotonin system particularly the hippocampus (memory)
- Can induce psychiatric disturbance in vulnerable individuals
- Idiopathic toxic response (not common but nasty)
 - Renal Failure
 - Rhabdomyolysis – Disintegration of muscle tissue

Cholinergic Hallucinogens

- **Muscarine**
 - Acetylcholine Agonist (muscarinic receptors)
- Found in mushrooms (*Amanita Muscaria*)
 - Psilocybin
- Trance-like dreamy state with visual hallucinations
 - peripheral effects: sweating, limb twitching, seizure activity
 - potent hallucinogen, induces actual hallucinations

Tolerance/Dependence

- Not significant producers of tolerance or dependence.
- No withdrawal.
- People and animals do not self-administer
- Problems related to the things people do while under the influence
 - Accidents
 - Suicide
 - Aggression/Violence
 - Toxic Reactions

History of Marijuana

- Oldest nonfood crop cultivated by man
- Originated in central Asia
- Cultivated & dispersed before written history
- 2700 BC first written record in China
 - For medicinal properties

History of Marijuana

- Major cannabis spread about 200 BC with Scythians
 - warlike Middle Eastern tribe, gave us word “cannabis”
 - used in cleansing ceremony after funerals
 - threw hemp seeds on heated rocks inside tents & inhale vapors

History of Marijuana

- Hebrews also used cannabis (Old Testament in Exodus)
 - God told Moses to make holy oil containing cannabis
- Most infamous use by Muslim sect founded by Hasan-Sabbah (Hashishin)
 - secret assassination
 - gave us words Hashish & assassin
 - drug induced visions of paradise

History of Marijuana

- France in mid 1800's with "Club des Hachichins"
 - writer Gautier reward to anyone invent new pleasure--given hashish by a doctor
- Group of writers/artists got together for kicks
- Victor Hugo, Alexander Dumas
 - consumed large quantities of hash-like material
 - wrote accounts of their experiences

History of Marijuana

- In U.S. primarily for rope (George Washington)
- Introduced by Mexican laborers early 1900's (group targeted by 1st laws)
- Smoked by racial minorities/ jazz musicians
- 1920's & 30's major attention - drug of violent crime & danger to society
 - Commissioner of Narcotics, Harry Anslinger - crusade against marijuana

History of Marijuana

1937 Marijuana Tax Act

- made possession of marijuana without having paid special tax illegal

Early 1940's

- NYC Mayor Fiorella La Guardia
 - set up commission of experts to determine consequence of marijuana use
 - Final report—marijuana fairly minor intoxicant w/few side effects even when used excessively

History of Marijuana

- Marijuana comeback: late 1950's to early 1960's
 - now most broadly used illicit substance in U.S.
 - 20% of Americans having tried
- Numerous state has compassionate use laws

Active Ingredients

Δ -9- THC also Δ -8-THC (lower quantities)

Cannabinol & cannabidiol

- not active in own right
 - **cannabidiol** - slows metabolism of THC increase duration
 - **cannabinol** - increases rate of metabolism
- both inhibit THC binding
 - increase brain THC
 - cannabidiol converted to THC when burned
 - THC converted to cannabinol with time
 - (refrigerate when not in use)

Pharmacodynamics/kinetics

- Primary route of administration - smoking
 - about 25-50% THC absorbed
- Also oral, through G. I. system
 - half as effective.
- Highly lipophilic - spread throughout body fat stores and easily crosses BBB & placenta

Preparations Used of Marijuana

- Marijuana - leaves, seeds, small stems from males/females
 - content 1 - 7 %, THC reported to have risen with time
- **Sinsemilla** –American marijuana cultivation technique
 - males removed from females prior to pollination
 - resin (thus THC) production increased - no seeds
 - content as high as 15 % (no pun intended)

Preparations Used of Marijuana

- Hashish** -processing of plant to yield dried resin
- large difference in how made
 - main idea - more concentrated THC content
 - resins scraped/ plants harvested (female)
 - beaten down/ rolled in carpets
 - leaf substance collected
 - placed in tubs/jars containing alcohol
 - evaporated off to concentrate - pressed to bars
 - content 5 - 20 %

Preparations Used of Marijuana

- **Hash Oil**-boil w\solvent, solvent then strained out
- THC concentration as high as 60 - 70 %
- Becoming more popular - ease of smuggling

Pharmacodynamics/kinetics

- Average "joint" 10 to 20 mg
 - 2mg smoked, 5 mg eaten - mild euphoria
 - 7 mg smoked, 17 mg eaten - perceptual & time distortions
 - 15 mg smoked, 25 mg eaten - hallucinations, delusions, distortions of body image

Routes of Administration

- Inhalation – Smoke
- Oral – Tincture, Eating, Tea
- Marinol – Synthetic THC pill form

Pharmacodynamics/kinetics

- Shows characteristics of sedatives, stimulants, analgesics, & 5HT hallucinogens - dose dependent.
- **Low/moderate** – “exuberant feelings of pointless hilarity & irrepressible mirth accompanied by...”
 - sense of well being, mild euphoria, relaxation of anxieties
- **High** -dreamy, carefree state with perception of expanding space & time (most commonly reported)

Pharmacodynamics/kinetics

- Enhancement of perceptions for both internal & external (sounds especially)
- May produce panic reactions, delusions & paranoia
- May be due illicit status – e.g. fear police will burst in
 - Specific to culture

Physiological effects of Marijuana

Physiological effects

- increase in pulse rate & slight drop in BP
- produces dry mouth & occasional dizziness
- reddening of eyes (dilation of vessels in cornea)
- No permanent adverse cardiovascular
 - but people with heart disease should abstain
- appetite increased

Mechanism of Action

- Mostly unknown until the late 1980's
- THC binds to cannabinoid receptors
- Anandamide is the NT for cannabinoid receptor
 - Sanskrit for bliss
 - Cannabinoid receptors in hippocampus, basal ganglia, cerebellum, and cerebral cortex
- No brainstem cannabinoid receptors, so vegetative functions are not affected directly by THC.

Side Effects of Marijuana

- THC suppresses immune system but not enough to increase risk of infection.
- Lowers testosterone levels & sperm count
- Crosses placental barrier
- Most severe side effects
 - respiratory - can lead to asthma & bronchitis
 - 1 joint equivalent to approx 4 cigarettes

Toxicity

- Almost impossible to OD
- THC not toxic
- Pot smoke contains more tar than cigarette smoke
 - Does one smoke the same
 - Cancer and respiratory possibilities

Tolerance, Dependence & Marijuana

Wide safety margin with an unknown LD

- Tolerance develops with heavy long-term use
 - (cross tolerance with sedatives - alcohol)
- Dependence unresolved issue
 - Mild withdrawal symptoms in humans with irritability, sleep disturbances, nausea, diarrhea, sweating, tremors, and salivation - 30 mg THC / 4 hrs / 10-20 days (unusual levels of intake)

Dependence

- At this point marijuana dependence seems to have more to do with HOST and ENVIRONMENT FACTORS

Medical Marijuana

- Analgesic
- Anti-emetic
- Anti-spastic
- Appetite Stimulant
- Glaucoma

Medical Marijuana

- Many state have compassionate use laws
 - California
 - Arizona
- Physicians “recommend” marijuana and patient buy it at buyers clubs.
- Potential revocation of medical license.

Mood Disorders

- Antidepressants
 - MAO Inhibitors
 - Tricyclics
 - Selective Serotonin Reuptake Inhibitors
 - Others
- Mood Stabilizers (Antimanic Agents)
 - Lithium Carbonate
 - Valproic Acid
 - Carbamazepine

■ Major Depression

- Mood disorder characterized by
 - Prolonged feelings of worthlessness and guilt
 - Disruption of normal eating habits
 - Sleep disturbances
 - General slowing of behavior
 - Frequent thoughts of suicide
- Common: ~6% of adult population
- More common in women than in men

ANTIDEPRESSANTS

Three Classes of Antidepressants

1. Monoamine Oxidase (MAO) Inhibitors

- Block the enzyme MAO from degrading neurotransmitters such as dopamine, noradrenaline, and serotonin

2. Tricyclic Antidepressants

- First-generation antidepressants with a chemical structure characterized by three rings that block serotonin reuptake transporter proteins

Three Classes of Antidepressants

3. Second-Generation Antidepressants

- Action is similar to first-generation antidepressants, but is more selective in its action on the serotonin reuptake transporter proteins; also called atypical antidepressants
- Selective Serotonin Reuptake Inhibitors (SSRIs)
 - Block the reuptake of serotonin into the presynaptic terminal

- Although antidepressants affect synapses very quickly, their antidepressive actions take weeks to develop
- Prozac, an SSRI, enhances neurogenesis in the hippocampus
 - Part of therapeutic effect?
- ~20% of patients with depression fail to respond to antidepressants, suggesting that other neurotransmitters are likely involved

MAO Inhibitors

- Accidental discovery
- 1950's-looking for treatment for TB
 - Ineffective, but elevated mood of patients
 - Patients became more active & more sociable
 - due to MAO inhibition
- MAO degrades 5-HT, NE & DA
- Leads to increased availability of transmitter for release

MAOI

- Use in late 1950's & ended in early 1960's
 - use ended due to side effect (death)
- MAO breaks down many chemicals including tyramine
 - Tyramine-present in cheeses, red wines, alcohol, smoked fish
 - MAO in liver breaks down tyramine
 - Causes a hypertensive crisis "cheese syndrome"
 - increased blood pressure-->stroke--> death
 - increased heart rate--> heart attack--> death

Tri-Cyclic Antidepressants

- Act as agonists to catecholamines
- No "cheese syndrome"
- Side effects major problem
 - Cardiotoxic
 - Sedative action
 - Block acetylcholine system-especially muscarinic receptors
 - blurred vision, dry mouth, urinary retention, constipation, mental confusion

SSRI

- Selectively block re-uptake of 5-HT
 - Work on DA and NE as well but very little
- Eliminate ACh effects
- No more effective than MAOI or tricyclics
- Better because there are fewer side effects
- On market since late 1980's & early 1990's
 - Fluoxetine - Prozac
 - Sertraline - Zoloft
 - Paroxetine – Paxil
 - Citalopram - Celexa

Others

- Bupropion (Wellbutrin)
 - No effect on either 5-HT or NE
 - Effective at blocking DA reuptake
 - May be similar action to cocaine
 - Lowers seizure threshold
- Nefazadone (Serzone)
 - 5-HT reuptake blocker
- Venlafaxine (Effexor)
 - 5-HT, DA and NE reuptake blocker

Treatments For Depression

- All of these compounds have little effect on 'normals' but are effective in depressives
 - May cause agitation, restlessness or anxiety
 - No abuse potential
 - Cognitive Behavioral Therapy is as effective and better in the long run.
 - Medications make good stabilizers
