Drugs of Abuse:
A Pharmacological Perspective

Bob Lyon, PhD
Procter and Gamble Health Care
Mason, OH

American Translators Association
San Diego, CA
October 26, 2012

Today's Presentation

- This presentation is a scientific background on the pharmacology and effects of abused drugs
- These drugs may have effects and/or side-effects that are dangerous
- Many of these drugs are illegal and can have harmful effects

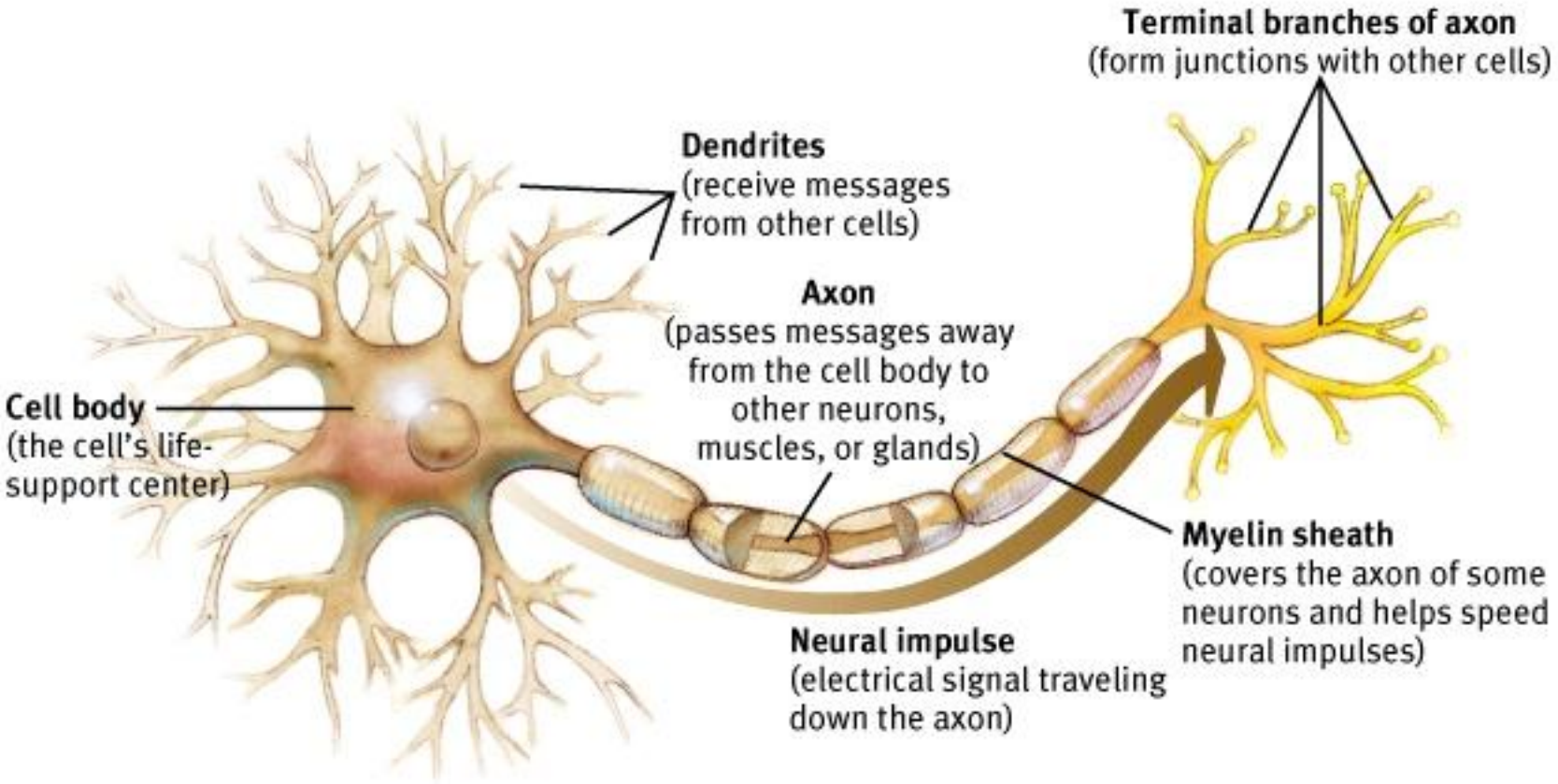
Agenda

- Terminology:
  - Nerve
  - Neuron
  - Nerve Terminal
  - Neurotransmitter
  - Receptor, Release, Re-uptake
- Drug Scheduling
- Designer Drugs
- Addiction, Dependence, Withdrawal
- Stimulants, Depressants, Hallucinogens

The human brain has over 100 billion neurons…the complexity is enormous. Our understanding is basic at best.

The Neuron (Central Nervous System)

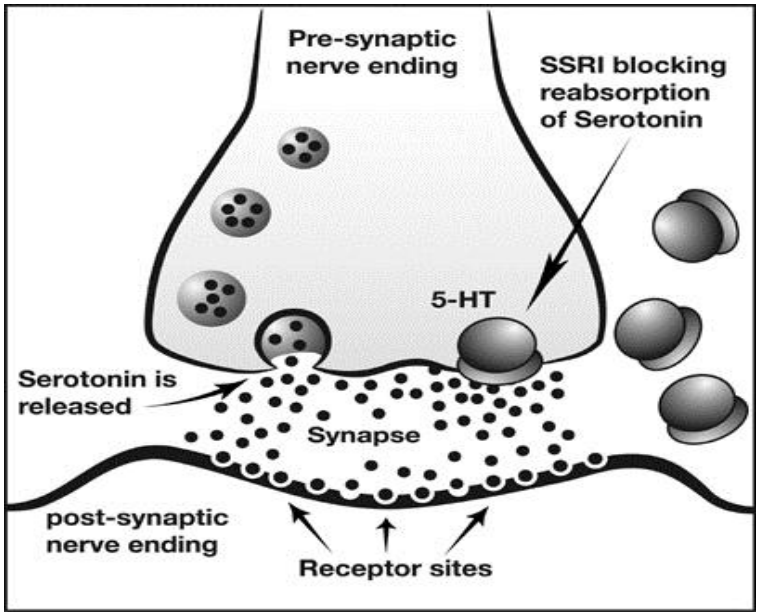
(How drugs work in the brain)



Neurotransmitters

(How drugs work in the brain)

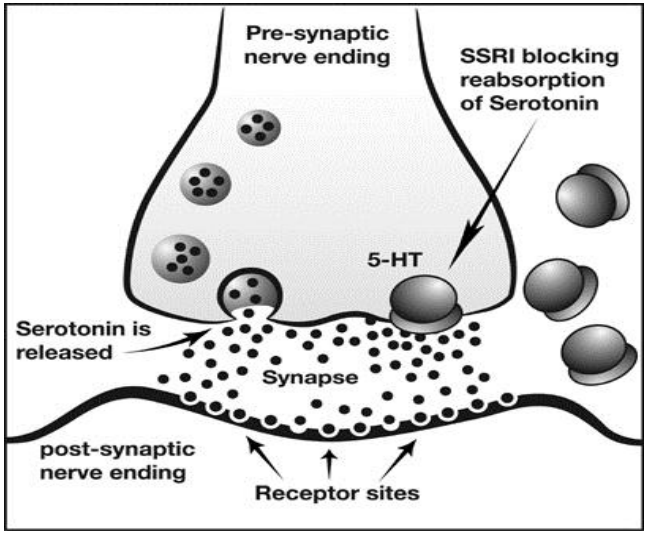
- Neurotransmitters are chemical signals:
  - Synthesized, stored and released in the nerve terminal
  - Includes Norepinephrine, Serotonin, Dopamine, Glutamate, Endorphins etc (> 100 neurotransmitters known)
  - Neurotransmitters are released into the synapse: Pre/Post Junctional
  - Neurotransmitter re-uptake sites and metabolism to stop effect
  - Drugs can mimic neurotransmitters or block their effect



Receptor and Drug Terminology

(How drugs work in the brain)

- Receptor:
  - Protein on cell surface or inside cell
  - Site of action of neurotransmitter/drug
  - Transmits the message to the cell
  - Pre-junctional vs post-junctional
  - Example: serotonin receptors
    - 5-HT2a receptors



- Agonist:
  - Stimulates receptor; mimics neurotransmitter action
  - Serotonin and serotonergic drugs

- Antagonist:
  - Blocks the action of a neurotransmitter or drug
  - Naloxone (opioid antagonist), blocks the mu opiate receptor

- Releasing Agents/Uptake Blockers

Drug Scheduling and Terminology

- Drug Use:
  - Drugs may have accepted medical uses and illegal uses
  - Prescription, Over the Counter and “Street” drugs

- US Drug Scheduling: Schedule 1-5 based on abuse potential and medical usefulness:

  - A Schedule 1 drug has high abuse potential without accepted medical use (e.g., Heroin)

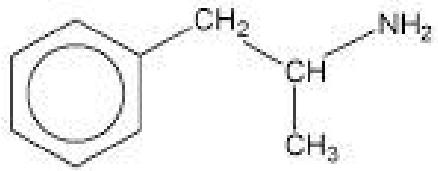
  - A Schedule 5 drug has low abuse potential and medical use (codeine)

  - An Over the Counter drug (OTC) is not scheduled

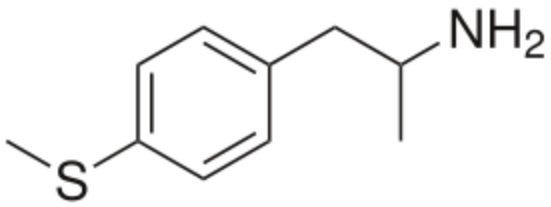
  - Some drugs (caffeine, nicotine, alcohol) are not scheduled

Designer Drugs

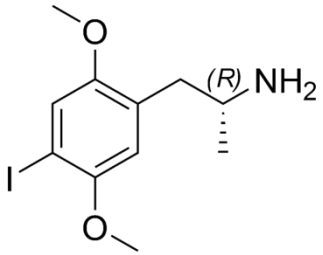
- Designer Drugs:
  - Chemical modification of a drug to avoid scheduling laws
  - Bath Salts, Synthetic marijuana, psychedelics



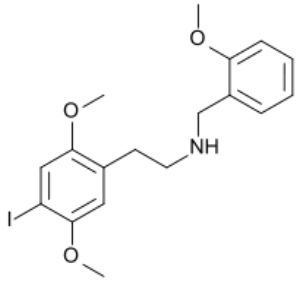
Amphetamine



4-methylthioamphetamine



DOI



25I-NBOMe

Additional Terminology

- Route of Administration: how the drug is taken into the body
- Drug Delivery Device: how the drug is delivered to the body
- Addiction: psychological craving for a drug/effect
- Dependence: lack of drug produces physical withdrawal syndrome
- Withdrawal: symptoms following cessation of drug
  - Caffeine, Marijuana? New Data
- Tolerance: need more of the drug to produce the same effects

Central Nervous System Stimulants

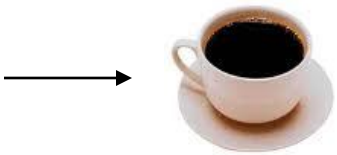
Central Nervous System (CNS) Stimulants

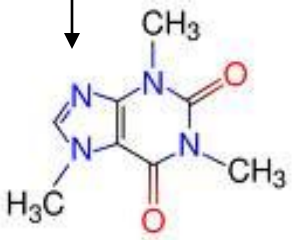
- Includes caffeine, nicotine, amphetamine, cocaine and bath salts
- Basics:
  - Induce temporary improvements in mental or physical function
    - High energy and focus
    - Decreased need for sleep
  - “Stimulate” as oppose to depress or “down” effects
  - Caffeine and Nicotine: not controlled or scheduled
  - Amphetamine and Cocaine: Schedule 2 drugs
  - Bath Salts: designer drugs (Schedule 1)
- These drugs interact with various receptors/neurotransmitters
  - Different effects/abuse potential

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
Adenosine		●	

CNS Stimulants: Caffeine

- Caffeine:
  - Source: the coffee plant



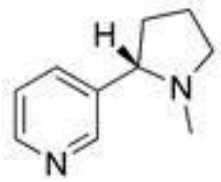


- Route of administration: drinks, foods, tablets
  - Pharmacology: Adenosine receptor antagonist
  - Effects: alertness, decreased fatigue
  - Side Effects: diuresis, nervousness, loss of sleep
  - Rapid tolerance, addiction, dependence: withdrawal syndrome
  - Not scheduled or controlled, sold freely

CNS Stimulants: Nicotine

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
Nicotinic Cholinergic	●		

- Nicotine:
  - Source: Tobacco plant



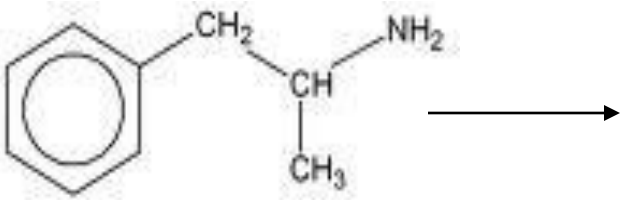
  - Route of administration: smoking, patch, gum
  - Pharmacology: nicotinic cholinergic receptor agonist
  - Effects: alertness, wakefulness
  - Side Effects: increased blood pressure and heart rate
  - Lung cancer and lung disease
  - Rapid Tolerance, addiction, dependence: withdrawal syndrome

- Nicotine is one of the most addicting substances known
  - As addictive as cocaine and heroin
  - Not scheduled, sold freely (age requirements)

CNS Stimulants: Amphetamine

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
	•	•	Dopamine Serotinin Norephinephrine

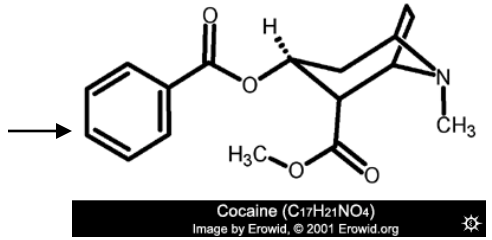
- Amphetamine (meth-amphetamine): crank, crystal:
  - Source: Illegal synthesis/pharmaceuticals
  - Routes of administration: oral, smoked, injection, snorting
  - Pharmacology: increases dopamine/norepinephrine in synapse
    - Releasing agent and re-uptake blocker
  - Effects: euphoria, alertness, increased energy
  - Side Effects: increased blood pressure/heart rate; decreased appetite
  - Long-term: psychosis, possible brain damage
  - Rapid Tolerance, addiction, dependence: withdrawal syndrome
  - Schedule 2 drug: medical use: ADHD and narcolepsy



CNS Stimulants: Cocaine

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
	•	•	Dopamine Serotinin Norephinephrine

- Cocaine (crack, snow, blow, nose-candy)
  - Source: coca plant
  - Routes of administration: snorting, oral, injection, smoking
  - Pharmacology: increases dopamine in synapse (uptake and release)
  - Effects: euphoria, energy, decreased appetite, increased focus
  - Side Effects: increased blood pressure and heart rate
  - Effects on the heart
  - Rapid tolerance, addiction, dependence: withdrawal syndrome
  - Schedule 2 drug: medical use as a local anesthetic



CNS Stimulants: “Bath Salts”

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
	•	•	Dopamine Serotinin Norephinephrine

- Latest “designer drug” trend
- Actives may include:
  - Mephedrone
  - Methylenedioxypyrovalerone
  - Methylone
  - Others?
- Trade Names: Ivory Wave, Purple Wave, Vanilla Sky
  - Source: Synthetic chemicals
  - Delivery: Snorting, smoking
- Effects: CNS stimulation, hallucinations (?): suicidal behavior
- These are not used for bathing, only labeled that way
- Synthesized in China/India, packaged in E Europe
- September 7, 2011: DEA emergency scheduling for 1 year
- Schedule 1 status is now permanent

CNS Stimulant Summary

- General stimulant properties:
  - Alertness
  - Wakefulness
  - Increased energy, decreased fatigue
- Mild to Extreme Stimulant Effects:
  - Caffeine to Cocaine/Amphetamine
  - Based on mechanism and systems effected
  - Dopamine/Norepinephrine are key neurotramsitters
- Caffeine and Nicotine: not schedules
- Cocaine and Amphetamine: Schedule 2
- Bath Salts: Schedule 1 (designer drug issue)

CNS Depressants

CNS Depressants

- Includes: alcohol, opiates/opioids, barbiturates, benzodiazepines

- Basics:
  - Reduce the function of or slow down parts of the brain/body
  - Analgesia, sedation, somnolence, relaxation, anesthesia
  - Usually opposite effects to the CNS stimulant class of drugs

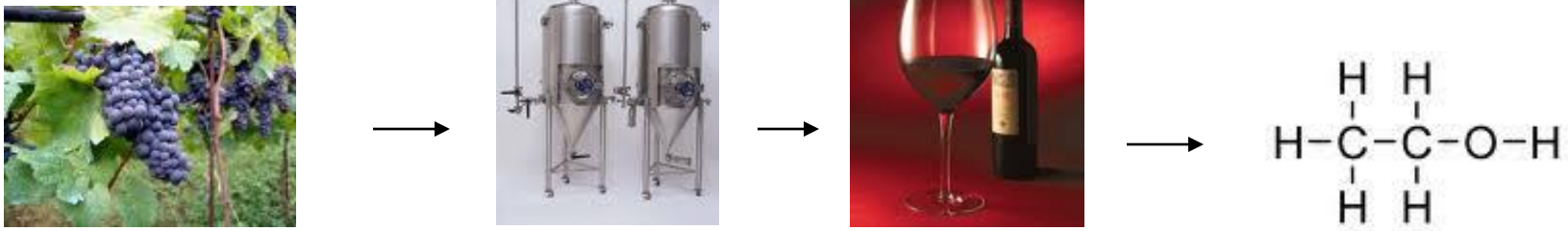
  - Alcohol: not Scheduled
  - Opiates/Opioids:
    - Heroin: Schedule 1
    - Morphine: Schedule 2 (used as an analgesic)
    - Codeine: Schedule 5 (used as an anti-tussive)
  - Barbiturates and Benzodiazepines: Schedules 2-4

- These drugs interact with a variety of receptor/neurotransmitter systems

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
GABA, NMDA		● (?)	

CNS Depressants: Alcohol

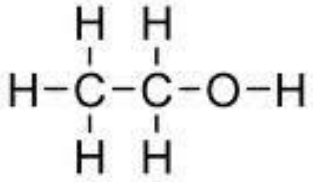
- Alcohol: Ethanol (ETOH)
- Most commonly used intoxicating substance
  - Usage as far back as 9000 BC
- Source: Fermentation of sugars into ethanol



- Routes of administration: oral (drinking)
- Pharmacology:
  - Effects on Acetylcholine, GABA, Serotonin and NMDA receptors
  - Exact mechanisms not fully understood: general depressant effect

CNS Depressants: Alcohol

- Effects (by dose-response):
  - Relaxation, talkativeness, euphoria (so-called “social lubricant”)
  - CNS depression
  - Nausea, vomiting
  - Impaired sensory and motor function, impaired thinking
  - Unconsciousness
  - Death



- Side Effects:
  - Birth defects (fetal alcohol syndrome)
  - Alcoholism (a disease)
  - Liver disease/failure

- Addiction, tolerance, dependence: withdrawal syndrome are known

Side Effects of Alcohol Use

Four Loco Product

Caffeine + Alcohol

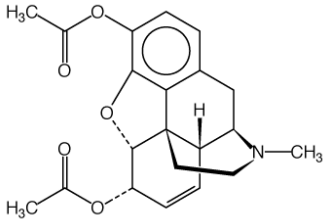
Banned

Opiates and Opioids

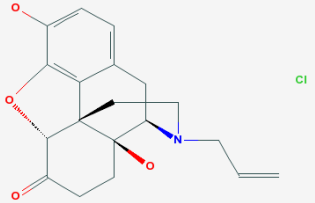
Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
Opiate (mu)	●		

- Opioid Drugs:

Morphine:
Agonist



Heroin:
Agonist



Naloxone:
Antagonist: Used in heroin overdose

Opiates and Opioids
Morphine, Heroin, Codeine

- Basics:
  - Opium: the sap of the opium poppy plant
  - Used medically and recreationally since 5000 BC
  - Sap contains the opiates morphine, codeine and thebaine
  - Opioids: compounds binding to the opiate receptors (agonists)
  - Heroin and other opioids synthesized from morphine

- Receptors:
  - Mu, delta and kappa opioid receptors

- Endogenous Substance/Transmitter:
  - Endorphins and Enkephalins
  - Endogenous opioids
  - Natural Analgesics

Opiates and Opioids: Heroin

- Slang:
  - Dope, Smack, Junk

- Routes of Administration:
  - Injection, Smoking
- Effects:
  - Euphoria, feeling of well-being, relaxation, sedation, analgesia
- Side Effects:
  - Constipation, blackout, over-dose: respiratory depression/death
- Tolerance/Addiction/Dependence:
  - Rapid tolerance/addiction/dependence: withdrawal syndrome
- Schedule 1 Compound: no accepted medical use

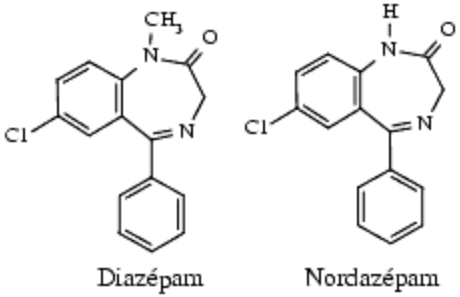
Opioids: Codeine, Oxycodone

- Cough Syrup Drinking (popularized by some rappers)
  - Some prescription cough medicines contain codeine
    - Codeine is a schedule 5 drug
  - Codeine is an opiate
    - It is metabolized to morphine in the body
  - All of the warnings on opiates apply

- Other Opiates:
  - Oxycodone: Prescription pain-killer: Percocet/Oxycontin
  - Highly addictive/dependency/withdrawal
  - Schedule 2 drugs
  - Major public health issue

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
GABA	●		

CNS Depressants: Other Pharmaceuticals



Diazépam Nordazépam

- Pharmaceutical (Rx) Products

- Barbiturates
  - Phenobarbital, pentobarbital
  - Pharmacology: GABA receptor agonists
  - Medical Use: anxiolytics, hypnotics (sleep-inducing), relaxation
  - Schedule 2-4 drugs

- Benzodiazepines
  - Have largely replaced the barbiturates
  - Librium, valium, rohypnol
  - Rohypnol: “roofies”: “date-rape” drug
  - Pharmacology: GABA receptor agonists
  - Schedule 4 Drugs
  - Addiction, tolerance, dependence: withdrawal

CNS Depressants Summary

- General CNS Depressant Effects:
  - Calming, relaxing, sleep induction, analgesia
- Wide Range of Effects/Properties:
  - Alcohol to Heroin
  - Based on system effected
- Alcohol: not scheduled
- Opiates/Opioids: schedule 1-5
- Barbiturates/Benzodiazepines: schedule 2-4

Hallucinogens:

Marijuana

Psychedelics/Dissociatives/Deliriants

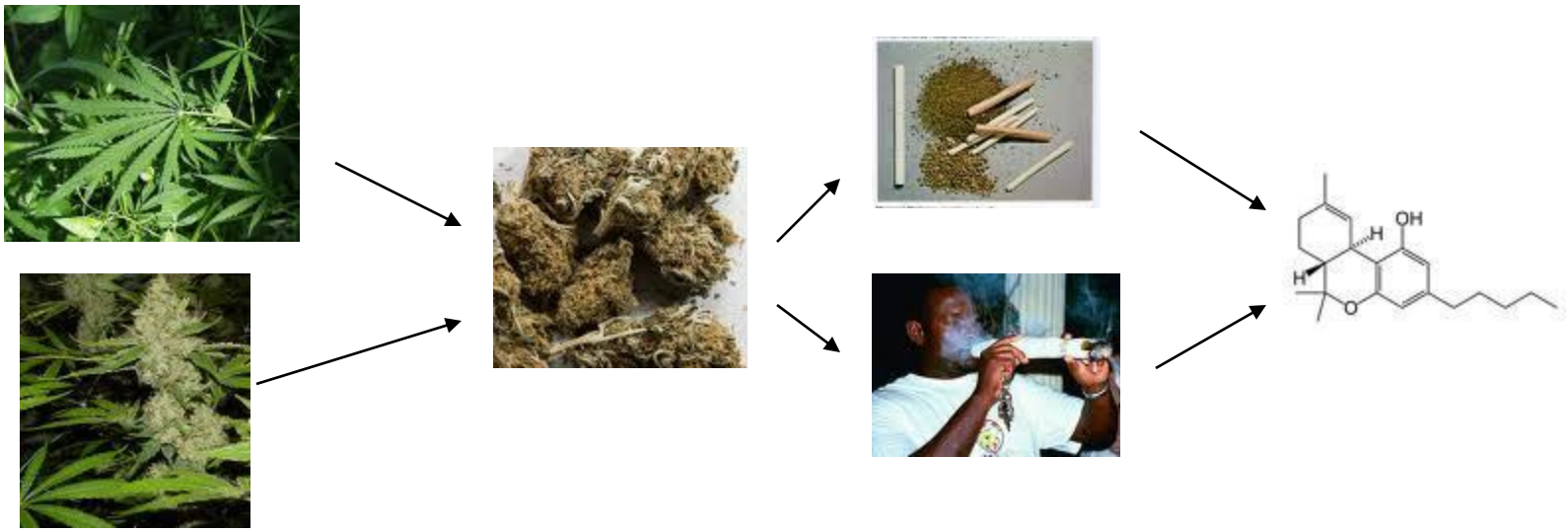
Hallucinogens
Psychedelics/Dissociatives/Deliriants

- Basics:
  - Mind-altering hallucinogens have been used for thousands of years
    - Used in Religious and Shamanic rites/ceremonies
  - "Hallucinogen" is largely a mis-nomer
    - A hallucination is something that has no basis in reality
    - Drug effect: change, enhancement or modification of normal perception
- Three Classes of "Hallucinogens"
  - Psychedelics: "classical" hallucinogens (LSD, Psilocybin etc)
  - Dissociatives: anesthetics (PCP, Ketamine, Dextromethorphan)
  - Deliriants: true hallucinogens? (Atropine)

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
Cannabinoid	●		

Cannabis: Marijuana

- Basics:
  - Classified as a mild hallucinogen
  - UN calls it the “most widely used illicit substance in the world”
  - Use goes back to at least 3000 BC
  - Delta 9-THC is the active chemical
  - At least 60 other cannabinoids are present (designer drugs)
  - Forms: Plant, Hashish, Hashish Oil
  - Sources:



Cannabis: Marijuana (THC)

- Routes of administration: smoke, oral
- Pharmacology:
  - Cannabinoid 1 and 2 receptors (CB1 and CB2)
  - THC is an agonist
  - Endogenous cannabinoid: Anandamide

- Effects:
  - Euphoria, laughter, relaxation, abstract thought, creativity, analgesia, slowing of time

- Side Effects:
  - Anxiety, coughing, dizziness, paranoia, increased heart rate, increased appetite, dry mouth, short term memory loss

- Schedule 1 drug: Can be addictive; tolerance develops
  - Recent Data: UK Study: clear withdrawal syndrome described

Synthetic Marijuana

- K2 or Spice
  - Appeared in 2004
  - Often sold as incense: head shops, gas stations
  - Actually contains synthetic cannabinoids
  - May be much more potent than THC
  - Has been reported to be highly addicting
  - Schedule 1 compounds
    - “Designer Drugs” to avoid scheduling laws

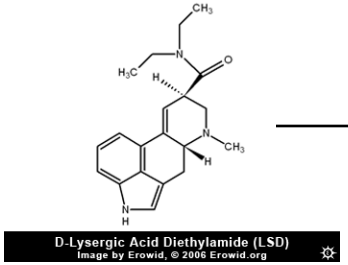
Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
5-HT2A Serotonin	●		

Hallucinogens: Psychedelics

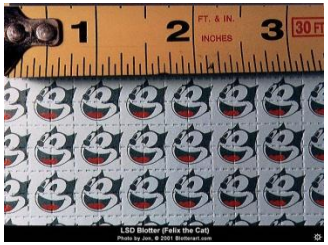
- Includes LSD, Psilocybin, Mescaline, DMT, 25I-NBOMe
- Routes of administration and Sources:
  - LSD: oral (blotter paper, liquid, tablets)
    - One of the most potent drugs known
    - Precursors occur naturally, LSD then synthesized in clandestine labs
  - Psilocybin: oral (usually as mushrooms)
    - Mushrooms grow naturally or are cultivated
  - Mescaline: oral (as peyote cactus)
    - Peyote is a naturally-occurring cactus
  - DMT (dimethoxy tryptamine): smoked (due to metabolism)
    - Amazonian tribe: ayahuasca to avoid metabolism
- Pharmacology: Serotonin 5-HT2a agonists
- Scheduling: All are Schedule 1 drugs (no accepted medical use)
  - Studies in alcoholism, spirituality, religious experience, depression
  - May find accepted medical use?

Psychedelics
LSD, Psilocybin, Mescaline, DMT

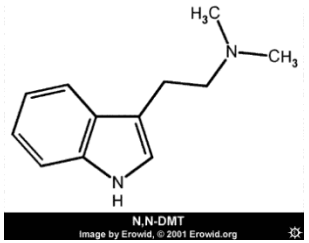
LSD



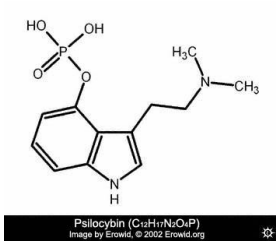
Blotter



DMT

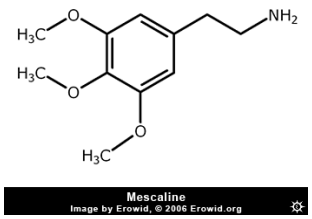


Magic Mushrooms Psilocybin



Peyote Cactus

Mescaline



NOTE: People have died from picking/eating poisonous mushrooms

Psychedelic Effects
LSD, Psilocybin, Mescaline, DMT

- Psychedelic effect as opposed to hallucinogenic effect
- Effect can be up to 8-12 hours (hence the name “trip”)

  – Profound alterations in perception
    - Effect of “set” and “setting” determine the “trip”
    - Vivid colors/patterns
    - Changes in thought patterns
    - Enhanced appreciation of music/art; enhanced spirituality

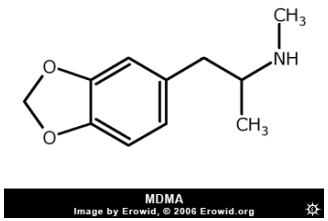
  – Side Effects:
    - Weakness, jaw clenching
    - Increased heart rate
    - Tremors, loss of sleep
    - Potential for psychiatric problems
    - Flashbacks: urban legend

  – Rapid Tolerance; no dependence or addiction

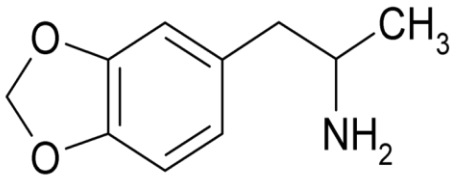
Other Psychedelics

- 5-HT2A Agonists:
  - 25I-NBOMe: phenylethylamine related to DOB/DOI
    - Relatively new “designer” drug, related to DOB/DOI
  - 2-CI: phenylethylamine related to DOB/DOI
    - Schedule 1
    - Known as “smiles”
- Serotonin Releasing Agents:

MDMA (ectasy)



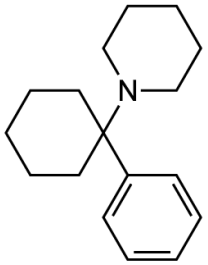
MDA



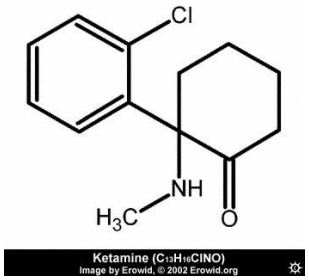
Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
NMDA		●	

Dissociative Hallucinogens

Phencyclidine (PCP)



Ketamine



Dextromethorphan

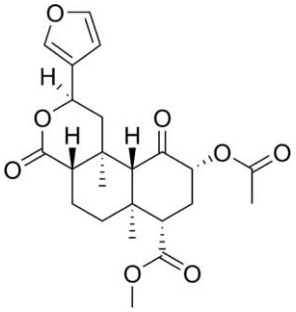
All are NMDA receptor antagonists
Produce a dissociative state (out of body experience)
PCP (schedule 2) ; Ketamine (Schedule 3)
Dextromethorphan is OTC

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
Opiate (kappa)	●		

Dissociative Hallucinogens
Salvia Divinorum

Salvia Divinorum:

- “Diviner’s Sage”, “Seer’s Sage”
- Used by Shamans in visionary healing rituals (Mexico)
- Active component is Salvinorin A: kappa opioid agonist
- Schedule 1 (varies by state)
- Kappa opioid receptor agonist



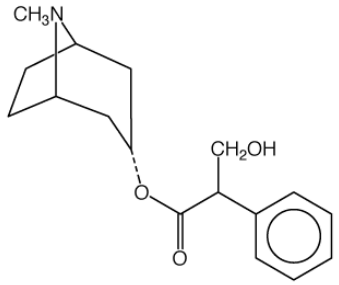
Hallucinogens: Deliriants

Receptor	Type of Action at Receptor Site		
	Agonist	Antagonist	Uptake/Release
Muscarinic cholinergic		●	

- Perhaps “true” hallucinogens
  - Visualizing things that are not really there
- Pharmacology: Muscarinic receptor antagonists
- Typified by atropine (schedule 4)

Deadly Nightshade

Jimsonweed



Atropine

Effects can be terrifying,
overdose can be fatal

Hallucinogen Summary

- Marijuana is considered a mild hallucinogen
  - Schedule 1 despite “medical marijuana” in some states
  - New data on possible withdrawal syndrome in chronic users
- Hallucinogens described in 3 categories:
  - Psychedelics, dissociatives, deliriants
  - All can have profound effects on perception
- LSD, mescaline, psilocybin are schedule 1 drugs
  - On-going clinical research into possible medical use

Summary/Main Points

- Drugs of abuse are chemical compounds that interact with specific receptor/transport/release systems in the central nervous system
- A variety of effects may be produced by these compounds, depending on the dose used and the specific system affected
- Many abused drugs have approved medical uses
  - Others are being investigated for possible medical use
- Most of the drugs discussed today are illegal and may be dangerous

Thank You!

Questions?

I’m glad to speak separately as well