Opiates

Psychology 472

Pharmacology of Psychoactive Drugs

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Drug Groups used for Pain Analgesics

1. Opioid ("opiate") analgesics
2. Non-opioid analgesic-anti-inflammatory analgesics (NSAIDs)
3. Drugs to increase analgesic effects
   - Antidepressants
   - Anticonvulsant
   - NMDA-antagonists (e.g., dextromethorphan)
   - Tetrahydrocannabinol (e.g., Sativex)

Naturally-Occurring Opioids

Two sources:

- Endogenous transmitters with morphine-like actions (e.g., endorphins)
- Opium poppy: morphine and codeine

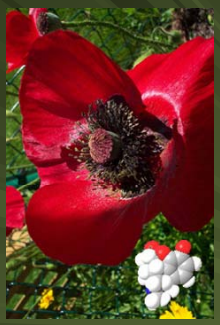
- All other opioids are either semi synthetic or totally synthetic.

Opiates

Natural plant product

- Opium comes from poppy plant,
  - Not the same variety as the garden plant.

- Difficult to synthesize in the lab



Opium Poppy

TERMINOLOGY

- **Opium**: Exeudate of the opium poppy
  - Contains morphine and codeine as natural products.
- **Opiate**: A drug derived from the opium poppy
  - (Morphine or codeine)
- **Opioid**: Agonist with morphine-like activity
  - - Synthetics

Narcotic:

- From *narcos:*
  - any sleep-inducing drug
- Today - An illegal drug

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Groups of Opiates

- **Pure Agonist**: Morphine, Heroin, Dilaudid, Numorphan, Demerol, Fentanyl, Oxycodone.
- **Partial Agonist**: Buprenorphine (Buprenex, also in Suboxone)
- **Mixed Agonist-Antagonist**: pentazocine (Talwin), Butorphanol (Stadol), N Nalbuphine (Nubain), Dezocine (Dalgan)

Antagonists

- Have affinity for receptors but is devoid of morphine action.
  - Especially Mu receptors
- **Pure Antagonist**: Naloxone (Narcan), Naltrexone (ReVia, Trexan, Vivitrol), Nalmefene (Revex)

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Background

- Are derived from the opium poppy or are synthetic copies
- Many uses
  - Relieve pain
  - Induce sleep
  - Reduce sensation
  - Pleasure

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SHORT HISTORY

- Is mentioned in recorded history around 3400 B. C. in Mesopotamia
- Is being used by Egyptians, Greeks, Europeans, Chinese, by 400B.C.
  - Primarily used in medicine
- 1500 began to be used for pleasure in India
  - Becomes very important in commerce

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1805

- Morphine was first isolated and perfected by Friedrich Sertuerner.
- Named after the god of Dreams and Sleep, Morpheus
  - Called it "Morphinum"

Opium Wars

- **March 18, 1839**
  By Chinese Decree, all traders are required to surrender their opium.
- The British respond with Warships and the First Opium War Follows. It ended in 1842 with the Chinese giving Hong Kong to the British.

1856-1860

- The British renew hostilities with the Chinese over Opium Trade (and Smuggling)
- Second Opium War occurs
  - French Aid of the British.
  - Ended with legalization of Opium Trade.

More History

- During the American Civil War, 400 000 soldiers became addicted to morphine
- 1874 Wright synthesizes Heroin
  - Used to treat opium and morphine addiction

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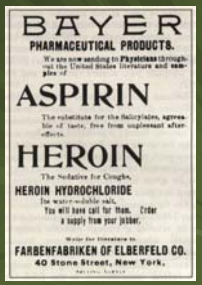
Laudanum: Medicinal Opium

- Commonly opium mixed with Red Wine or Port.
- Potentially dangerous if not properly mixed or if too much opium was present.

- Used in all sorts of medicines (OTCS) and products



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Legal Issues arise…

- The Harrison Narcotics Act passes in 1914 in attempts to end drug abuse (particularly of Heroin) It requires doctors, pharmacists and others who prescribed narcotics to register and pay a tax.
- This was not the first attempt to legislate drugs or to tax the use, just the most successful.

Opiate Receptors

- Approximately 17 have been reported
- Four main groups
  - Mu (μ),
  - Kappa (κ),
  - Delta (δ)
  - Nociceptive
- Others include
  - Epsilon (ε), Lota (ι) , Lambda (λ) Zeta (ζ)
- Includes subgroups (e.g. μ_1 , μ_2, μ_3)

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Response Depends on the Receptor Activated

- Mu 1
  - Supraspinal analgesic properties
    - Effects occur above the spinal cord
- Mu 2
  - Respiratory Depression
  - Dependence
- Kappa Receptor
  - Sedation
  - Spinal Anesthesia
- Delta
  - Site for endogenous opiates
  - Dependence

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More Examples

- Mu and Delta 1
  - Agonists activate mesolimbic dopamine system
  - Get a rewarding effect,
- Delta 2
  - Agonists use non-dopaminergic system
- Kappa
  - Activation suppresses physical and psychic dependence of mu and delta agonists
- Delta
  - Activation increase the dependence of Mu agonists.

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Many Products Contain Opium

- Opium
- Morphine
- Codeine (Methylmorphine)
- Demerol (**Meperidine or Pethidine)**
- Heroin (Diacetylmorphine)
- Hydromorphone (Dilaudid)
- Darvon/Darvocet
- Fentanyl
- Percocet
- Others
- http://www.opiates.com/opiates/opiate-library.html

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Opiate Types

- Biologically active opiates
  - Morphine, codeine, thebaine,
- Semi-synthetic opioids
  - Dilaudid, Hydrocodone, Percocet, Heroin, oxymorphone, desomorphine,, nicomorphine, dipropanoylmorphine, benzylmorphine and ethylmorphine and buprenorphine;
- Fully synthetic Opioids
  - fentanyl, pethidine, methadone, tramadol and dextropropoxyphene;

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Endogenous Opioids

- Are produced naturally in the body
  - Endorphins
  - Enkephalins
  - Dynorphins
  - Endomorphins.

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Other Compounds that bind on Opiate Receptors

- Salvinorin A is a K- receptor agonist
  - No real analgesic effects
  - Classified as a hallucinogen
- Dextromethorphan
  - Has no analgesic effects
  - Used in cough medicines

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Actions of Opiates

- Analgesia
  - Usually from opiates acting in the brain and/or the spinal cord
  - Can also impact other areas as well.
- Reduce thalamocortical processing and higher CNS functions.
- Inhibits (hyperpolarizes) neurons.
- Acts presynaptically on glutamate neurons to inhibit glutamate release

More Actions

- Respiratory depression
  - This is what kills you from an overdose/sedation.
  - Decreases respiratory center's sensitivity to higher levels of carbon dioxide in blood.
- Depresses the cough reflex
  - Antitussive action can be separated from other actions
- Decreases nausea and vomiting
- Causes constipation
  - Used as a last resort for major diarrhea

More Action

- Pupil constriction (miosis)
- Euphoria
  - Reduces the inhibitory effect of GABA on dopamine neurons

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Overall Effects on the Body

- Impact all muscles
  - Skeletal, heart
- Also Impacts lungs, brain, and eyes
- Muscles lose their ability to contract over time
- Cough and nausea centers are suppressed
- Digestive system slows down

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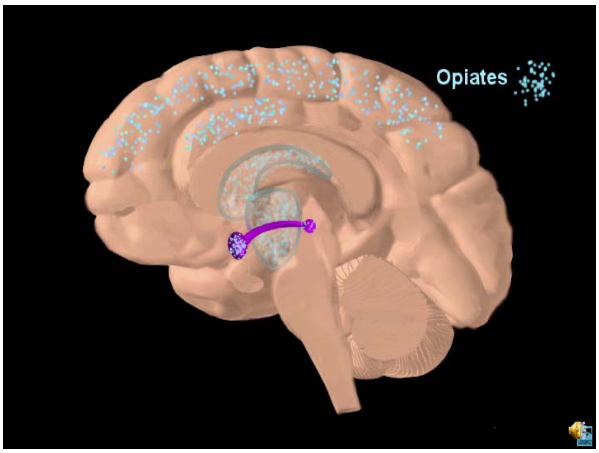

Opium

- O.P.", "hop", "midnight oil", "tar", "dope", and "Big O
- Brownish, tar-like substance
- Usually smoked (Use an opium pipe)
  - Active alkaloids (morphine) are vaporized
  - Then inhale the vapors
- Not used as much today
  - Other metabolites (morphine, heroin) are more popular

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Morphine

- Most refined form of Opium
- Taken by injection or orally
- Comes in liquid or pill form
- Common in the 60's and 70's, use decreases since the 80's
  - Hard to get
  - Replaced by synthetic opiates

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Some Slang Terms

- M, glad stuff, happy stuff, happy powder, white nurse, red cross, first line, God's Own Medicine, Vitamin M, Big M, Emma, Emmy, Miss Emma, Lady M, white lady, cube, cube juice, mo, morf, morph, morpho, mofo, hard stuff, shit, dope, dry grog, white merchandise, uncle, Uncle Morphy, morphy, coby, cobics, gold dust, monkey dust, number 13, unkie, mojo, needle candy, others.

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Pharmacokinetics

- Poorly absorbed when taken orally
- For users
  - Smoked or Injection preferred method
- Slowly crosses the blood-brain barrier.
- Achieves same level in fetus as in pregnant mother

Actions

- Decreases pain
  - Morphine and friends are unbeatable at this time
- Alters mood, reduces anxiety, creates euphoria
- Cough suppression
- Miosis
- Causes sleep
- Causes decreased gastrointestinal motility
  - Decreases diarrheal
  - Used as a last resort (important for cholera)
- Side effects
  - Nausea, vomiting
  - Respiratory depression

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Metabolization

- Metabolized to an active metabolite: morphine-6-glucuronide.
- Both have half-lives of about 3–5 hours.
- With impaired renal function can accumulate the active metabolite and can become toxic.

Withdrawal

- Similar to other opiate withdrawal
  - Restlessness, drug craving, sweating, extreme anxiety, depression, irritability, fever, chills, retching, panting, cramping, insomnia, explosive diarrhea, intense aches and pains
- Not life-threatening, but can seem unbearable.

Heroin (Diacetylmorphine)

- Comes in different colors
- Rapidly crosses blood-brain barrier; smoked, snorted, or injected.
- Slang terms
  - Dragon chasing" (heating of heroin with barbital on a piece of foil),
  - Madak and "ack ack" (smoking of cigarettes containing tobacco mixed with heroin powder)
- Metabolized to monoacetylmorphine, morphine, and codeine.

Slang Terms for Heroin

- Smack, gear, golden brown, brown, dope, stuff, crap, shit, horse, white horse, charlie horse, chick, brother, antifreeze, Aries, Aunt Hazel, birdie powder, bird shit, bird, boy, bomb, Witch Hazel, sweet Jesus, scat, blanco, chica, cheva.
- Older terms H, horse, harry
- Word “Heroin” usually only by people working in criminal justice system and pharmacology classes.

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THE RITUAL

- BLACK TAR-MEXICO
- ONE TENTH OF A GRAM A HIT
- THE WORKS

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Pharmacokinetics

- IV or smoking are most common methods of ingestion
  - Intravenous injection = slamming, hooting up").
- Intravenous injection
  - Provides the most intense rush
  - Occurs within seven to eight seconds.
- Smoking
  - Is becoming more popular
  - Purity levels are higher
  - Decreased risk for BBPs
  - Reaches peak effects within 10 to 15 minutes.

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Withdrawal

- Usually begins in 6 to 24 hours of discontinuation of the drug
- Similar to other opiates discussed
  - Sweating, anxiety, depression, general feeling of heaviness, cramping, excessive yawning or sneezing, tears, sleep difficulties, cold sweats, chills, severe muscle and bone aches; nausea and vomiting, diarrhea, cramps, fever

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Hydromorphone (Dilaudid, Palladone)

- 10 times as potent as morphine
- Considered the gem of opiates
- Dilaudid dose = 1–2 mg
- Effects in 30 to 60 minutes
- Metabolized in the liver,
- IV half-life about 2 hours.

Slang

- Dillie,, Delilah, D, dilly, dill, K1, K2, K3, K4 K8, M8, Big D, others

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Side Effects

- Similar to other opiates
- Light-headedness, dizziness, sedation, constipation, nausea, vomiting, sweating, others

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Withdrawal

- Begins within 24 hours after the last dose
- Increase in severity over the next 72 hours. Most gone after 3-5 days,
- Some symptoms
  - Like other opiates discussed
  - Restlessness, yawning, sweating, chills, diarrhea, irritability, anxiety, joint pain, weakness, abdominal cramps, insomnia, nausea and vomiting, others

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Meperidine (Demerol)

- 1/10th as potent as morphine
- Short action, rapid onset of withdrawal
- Exerts more excitatory effects than morphine because of active metabolite, normeperidine
  - Causes tremors, delirium, hyperreflexia, convulsions.
- Both substances accumulate in persons with reduced renal function.

Oxycodone and OxyContin

- Used to treat chronic pain
- OxyContin
  - Is the brand name of a time-release formula of oxycodone
- Metabolized by cytochrome P450 enzyme system in the liver,
  - Can have drug interactions
  - Issues with alcoholics
- Legally sells for $.10 per mg. Selling illicitly for $1 per mg.

Side Effects

- Like other opiates
  - euphoria, memory loss, constipation, fatigue, dizziness, nausea, lightheadedness, headache, dry mouth, anxiety, others
- Can have withdrawal symptoms like other opiates

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Fentanyl and Derivatives

- Fentanyl, sufentanil, alfentanyl and others
- Called China White
- Is a White Powder
- Rapid onset and short duration of action
  - Rapid addictive properties
- 100 times stronger than morphine
- Can be 100-20,000 times stronger than heroin
  - Under right conditions, one dose size of a salt grain can kill 30 people
- Effects and side effects similar to other opiates
- Often sold in patches

Methadone

- Synthetic Opiate
- Is long lasting
- Uses
  - Treating chronic pain
  - Heroin addiction
    - Taken orally usually with fruit juice
    - Reduces craving and withdrawal
    - Lasts up to 72 hours
- Is very addictive

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Uses

- Two uses:
  - Prevention of withdrawal in opioid-dependent persons (e.g., methadone maintenance programs)
- Federal regulations clearly differentiate these uses and who can prescribe.

Propoxyphene (Darvon)

- Structurally similar to methadone
- Less potent than codeine; more potent than aspirin
- Orally, not much potential for abuse
- Opioid-like at high doses, intravenous

Partial Opioid Agonists

Buprenorphine (Buprenex)

- Partial mu agonist
- There is a ceiling to the respiratory depression and the "high."
- Long-acting, 24 hours
- Very hard for naloxone to compete with it.
- May be an alternative to methadone for treating addiction.

Tramadol (Ultram)

- Another Partial Opioid agonist
- Partial agonist at mu receptors.
- Blocks reuptake of serotonin and nor epinephrine,
  - Has antidepressant effect.
- Many side effects: drowsiness, dizziness, nausea, vomiting, constipation, headache

Mixed Agonists-Antagonists

- Agonists at one receptor; antagonists at a second receptor
- Produce analgesia by
  - Agonistic action at kappa receptors,
  - Weak or antagonistic action at mu receptors.
- Low doses cause moderate analgesia, higher doses not much more.
- Side effects:
  - Dysphoria, anxiety, hallucinations.

Some Mixed Agonists-Antagonists

- Kappa agonists, poor mu agonists, even mu antagonists
  - Nalbuphine (Nubain)
  - Pentazocine (Talwin)
  - Butorphanol (Stadol)
  - Dezocine (Dalgan)

Opiate - Related Drugs

- Dextromethorphan
  - Is and OTC cough suppressant
- Clonidine
  - Relieves some withdrawal symptoms
- Naloxone (opioid antagonist)
  - used for overdoses)

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Tolerance to Opiates

- Increases metabolism at neuronal and liver levels
- Get up regulation of receptors
- Alters brain biochemistry

- Result - Tolerance

- USERS ALSO BECOME CROSS TOLERANT

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WITHDRAWAL

- Physical
  - Described with most drugs
- Psychological
  - Depression
  - Mood swings
  - Hypersensitivity to pain
- Withdrawal symptoms are usually NOT life threatening
- Feel like a extreme case of the flu
- Can cause to use again

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Conclusion

- Lots of different types of Opiates
- Lots of different effects
- Need to consider other drug use when users are taking opiates
- Look for withdrawal effects when clients are in treatment

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