

- We are moving on to a new category of drugs whose effects, superficially, may look similar to those of the CNS depressants, but the drugs are, in fact, a completely different pharmacologic family.

Opioid Analgesics (or Narcotic Analgesics)



- ◆ Beware of the term "narcotics" as used by law enforcement/drug enforcement agencies- it is not limited to this pharmacological category. Usually refers to any illicit drugs in that context.

- Natural source = *Papaver somniferum*
- (the opium poppy)
 - The sap from its seed capsule= raw opium, which contains:
 - *morphine ("prototype" or model opioid) (extracted from opium in 1803; named after Greek god of dreams)
 - *codeine (1/10-1/12 as potent as morphine)

Collecting the Raw Opium



<http://www.youtube.com/watch?v=8GmPgx6d2A>

Overview



Main effects

- Euphoria
- Sedation
- Constipation, nausea
- Analgesia
- Pupil constriction
- Eliminates cough
- Slows respiration

A few
more
details



Medical Uses for Opiates

- Our strongest analgesics
- Antitussive (anti-cough)
- Treat diarrhea
- Detoxification of narcotic addicts



- Most widely used medical opioid because of its lower potential for abuse (but dependency possible)
- Often combined with aspirin or acetaminophen
- SSRI interaction can block its pain relief
- 1 in 10 are rapid metabolizers

Chemically Altered Naturals or “Semi-synthetics”

- *heroin (or diacetylmorphine) (2-3 x as potent as morphine)
- *oxycodone (Percodan; Oxycontin (a timed-release form lasting 12 hrs) (2-6x)
- * hydrocodone (e.g.Vicodin) (1/10x)
- hydromorphone (Dilaudid) (6-10 x)



“Brown Sugar, Shit, H, Horse...”



heroin



The potent, nearly pure heroin available today produces powerful effects even by the [nasal route](#), luring in users who would have avoided the intravenous route.

<http://www.youtube.com/watch?v=NkvB3NzfdFo>



Totally Synthetic Narcotics (and the start of the use of the term **opioid**)

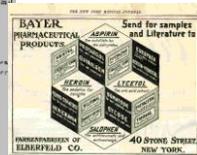
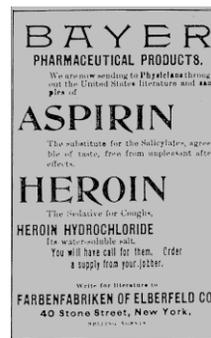
- *methadone (Dolophine) =
- mepiridine (Demerol) (1/10-1/5)
- propoxyphene (Darvon, Darvocet) (1/15) banned 11/10
- pentazocine (Talwin)
- *fentanyl (Sublimaze) (100x)
- A variety of illegal street analogs of fentanyl and mepiridine (“designer drugs”)

Opiate Use in the US

- unregulated before 1900’s
- 1800’s -sold by Sears, drug stores, mail order & by traveling salesmen selling patent medicines
- most common users were middle class women; even children were given opiates to sooth teething etc.
- hypodermic invented in 1856 - opiates were widely used during the Civil War to relieve pain as well as diarrhea

History (continued)

- 1898 Bayer Labs introduced heroin as a non-addicting substitute for codeine!!
- (in 1957 similar claims made for Darvon)
- By 1900 ~250,000 dependent, possibly 750,000 using in US
- After Harrison Act of 1914 demographics of use changed (use of black market drugs by urban young males)



2009 DAWN Data ----- # of ER Visits & #/100,000 pop

Alcohol in Combination with Other Drugs ¹	519,650	169.3 Underage
Drinking ^{2*}	199,429	227.2
Illicit Drugs	973,591	317.1
Cocaine	422,896	137.7
Marijuana		376,467 122.6
Heroin	213,118	69.4 Pharmaceuticals
1,244,679	405.4 Pain Relievers	595,551 194.0
Narcotic Pain Relievers	397,160	129.4
Oxycodone Products	175,949	57.3
Hydrocodone Products	104,490	34.0
Drugs to Treat Insomnia and Anxiety	433,600	141.2
Benzodiazepines	373,328	121.6
Antidepressants	104,940	34.2

Opioid total ~ 800,000

Lots of Opioids--Different Categories

- Pure opioid agonists- fit & fully activate opioid receptors
- Partial agonists – only partly activate receptors so not as effective
- Mixed agonist/antagonist – activates some receptors but blocks others, so not as effective
- Opioid Antagonist- fits but doesn't activate opioid receptors, blocking them
- BUT: also depends on who's taking drug

Pharmacologically assisted gradual withdrawal

- Gradual withdrawal → milder symptoms
- Substitute a legal, orally effective opioid & decrease dose over 5-10 days. (buprenorphine, methadone)
- In mild addictions non-narcotics (like clonidine) may be sufficient to ease body symptoms and produce some relaxation.

Endogenous Morphine-Like Substances (or "Endorphins") & Opioid Receptors

- Our bodies produce their own pain relieving, euphoria producing substances (**beta-endorphins, enkephalins, dynorphins**) which act on specific receptors (**opioid receptors, several varieties**).
- **Opioid analgesics** work because they can also activate these receptors, especially the **mu** variety of receptors
- With regular use of opioids, production of our own pain relieving substances decreases. This tolerance occurs rapidly.

Opioid Withdrawal

- Dysphoria and intense craving for relief
- Insomnia, irritability, restless
- Sniffles, shits, "explosive diarrhea"
- Muscle spasms ("kicking the habit")
- Agony, cramps, bone & muscle pain
- Yawns, fever, shivers, goosebumps ("cold turkey"), stimulates hypothalamus
- Not life-threatening except in very rare cases, but very uncomfortable.
- Altho the worst is over in 5-7 days, sleep, discomfort and bodily abnormalities can persist for up to 6 months

"Opioid Antagonists"

- Drugs fit opioid receptors & block receptors, **preventing** other opioids from binding to receptors: "narcotic antagonists"
 - *naloxone (Narcan) (injected & short half-life)
 - *naltrexone (ReVia, Trexan) (effective orally)
 - nalmefene (Revex) – injected, longer acting
- We already mentioned narcotic antagonists are effective reducers of relapse in alcoholics.
- Several other medical uses for these drugs →

Rapid Anesthesia-Assisted Detox (RAAD)

- Under general anesthesia addict given sufficient antagonist (like naltrexone) to block all opiate receptors & withdraw the user within hours
- Clonidine is given to prevent anxiety and hypertension
- (Normally narcotic antagonist would cause a sudden extreme withdrawal)

New Developments

- Long-acting injectable naltrexone (Vivitrol) (lasts 4 weeks)
- Implantable naltrexone pellets for months of release
- Opioid antagonists that do not cross BBB are used to reverse constipating effects of narcotics (Entereg, Relistor) in medical patients, but still permit analgesic effects

Another Use for Antagonists: Antidote for Overdose

- Naloxone injections (Narcan) can immediately reverse an opioid overdose
- Can also reverse the effects of opioids on a baby born to a mother who was using.
- Shorter time course (15-30 minutes) than the drugs it is reversing so needs to be re-administered at intervals
- (also recall their use for benzo overdose)

Post-Detox Use of Opioid Antagonist

- If recovering addict relapses while taking antagonist, they won't experience opioid effects
- Naltrexone (Trexan, ReVia) thus provides a "crutch" but only works in highly motivated individuals (e.g. addicted healthcare workers wanting to keep their job, parolees wanting to avoid prison) who will keep taking med (maybe 10% of those in treatment).
- Some of these individuals have stayed on antagonist for 10-12 years.

Uses Under Investigation

- Narcotic antagonists may decrease:
 - Self-injurious behaviors like cutting
 - Compulsive gambling

Naloxone to Deter Abuse

- May be added to orally administered opioid analgesics to prevent I.V. abuse. Naloxone not absorbed when taken orally or sublingually. If the oral drug is crushed & injected naloxone will block the opiate effects.
 - Talwin NX (pentazocine + naloxone)
 - Suboxone (buprenorphine + naloxone)
 - Embeda (morphine + naloxone)

Heroin Abuse Risks

- **Street drug risks:**
 - unknown dose; risk of toxic impurities
 - don't know what it is cut or mixed with
- **Route of administration risks**
 - dirty needles transmit disease
 - inflamed, infected, collapsed veins
 - risk of injecting dirty drug
- **Muffled body warning system**
- **Tolerance decreases safety margin**
- **Cost promotes illegal activities**

“Harm-Reduction” Approaches

Attempt to avoid these harmful risks. If abuse is going to occur, at least make that abuse less harmful to the individual & society.

Methadone Maintenance

- Provide a safe, cheap source of narcotics to avoid health & criminal/social problems of heroin; maintain daily contact. Best programs provide counseling/support services too.
- Methadone is effective orally & some may get by with daily dose. If user seems stable they may be given a few days worth of methadone
- **Buprenorphine (Subutex)** only needs to be taken 3x/week and it is the only maintenance drug that can be legally prescribed by a regular physician
- “Bu” also available as patch, a sublingual, or a monthly injection and **anti-abuse combo with naloxone**
- ~70% success, but some users drop out- they miss the rush & the culture

Methadone Maintenance



Example of the Harm Reduction Approach: Needle Exchange



Constant Battle for Funding

