Opioids:
Understanding the Basics

March 26, 2018

Amber L. Schilling, PharmD

Overview

- Historical Context
- Laws
- Pharmacology
- Dependence & Addiction

Historical Context

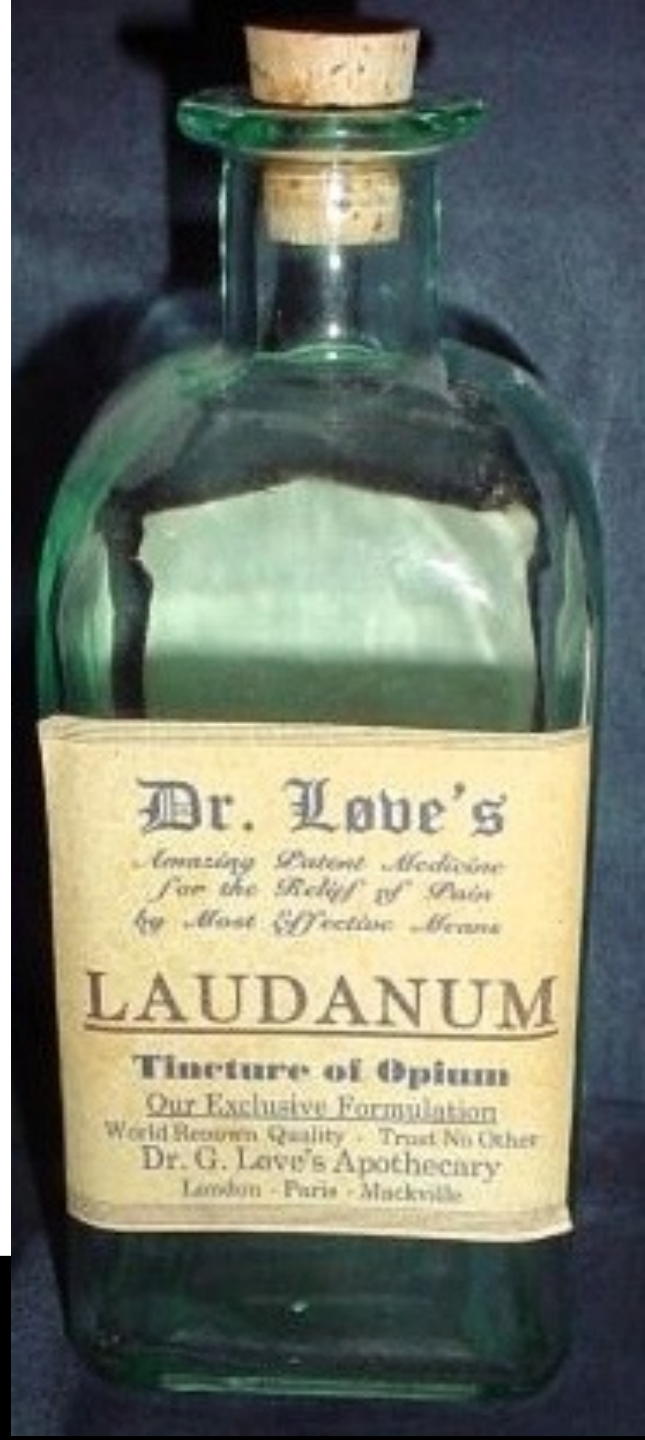
- *Papaver somniferum* = “opium poppy”
  - somniferum < Latin < “sleep bringing”
  - Flower (red, pink, or white petals)
  - Fruit (seed pod)
    - Incision produces white latex (“opium”)
    - Naturally-occurring alkaloids (“opiates”)
    - Morphine (10-14%)
    - Thebaine, Codeine, Papaverine, Noscapine, and Oripavine
    - Seeds contain very little opium

Historical Context

- Opium < Greek < “juice”
  - Juice or latex from seed pods

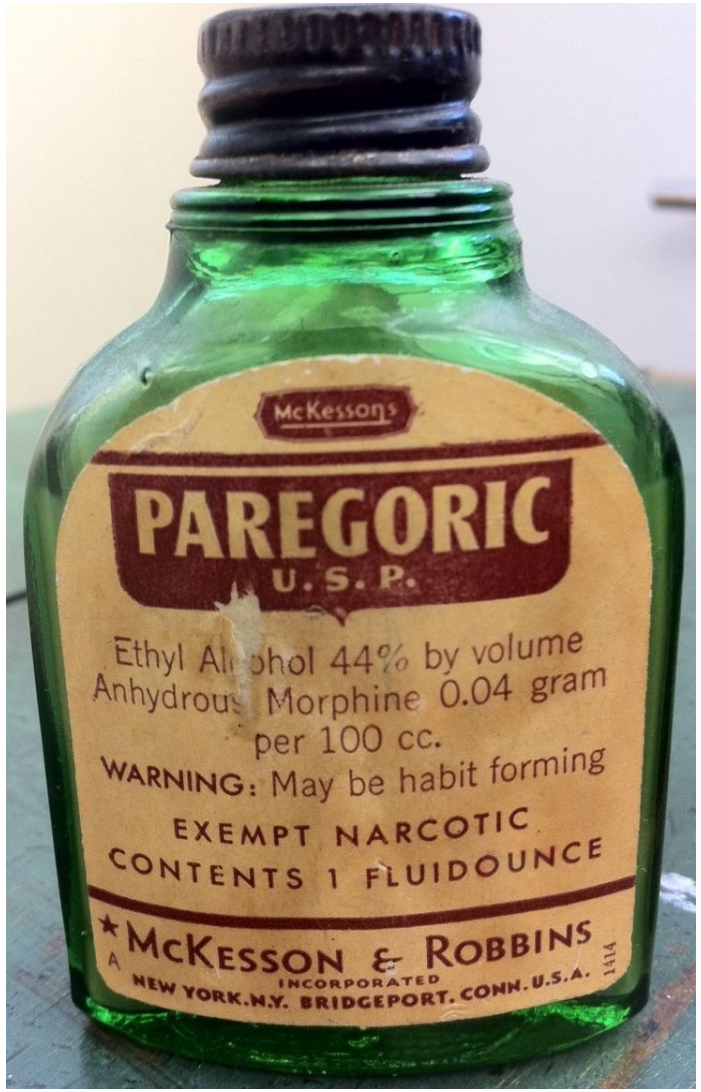
Historical Context

- 3500 BC
- 1500's
  - Swiss-German Alchemist
  - Opium tincture (opium latex + ethanol)
  - Laudanam < Latin < "to praise"
- 1660's (-- 1914)
  - Laudanam widely available w/o prescription
  - Analgesic (headache, toothache, menstrual cramps)
  - Sleep-aid (fussy infants)
  - Anti-diarrheal
  - Anti-tussive
  - High Social Circles



Historical Context

- Early 1700's (Netherlands)
  - Paragoric
  - Opium tincture plus camphor
  - Teething
  - Anti-diarrheal
  - Asthma
  - Common household remedy (18th-19th centuries)

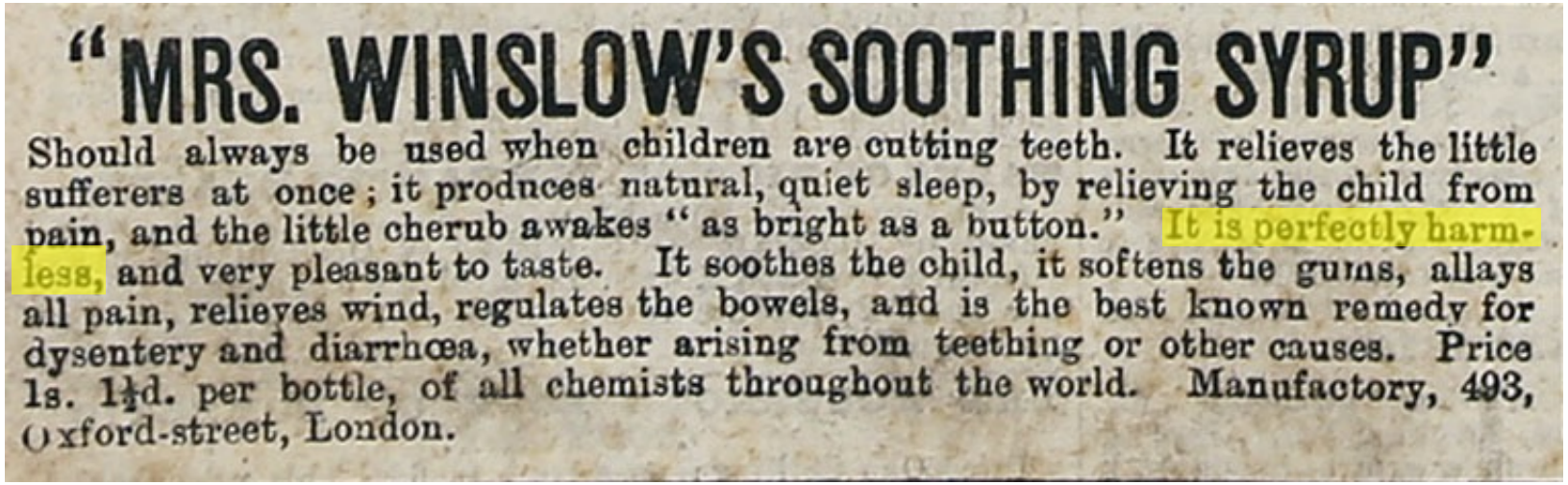


Historical Context

- 1805 (Germany)
  - Crystalline morphine isolated from the poppy plant
  - “morphium” < Morpheus < Greek god of dreams

Historical Context

- Civil War (1860's)
  - Morphine used extensively for battle injuries
  - Many became addicted



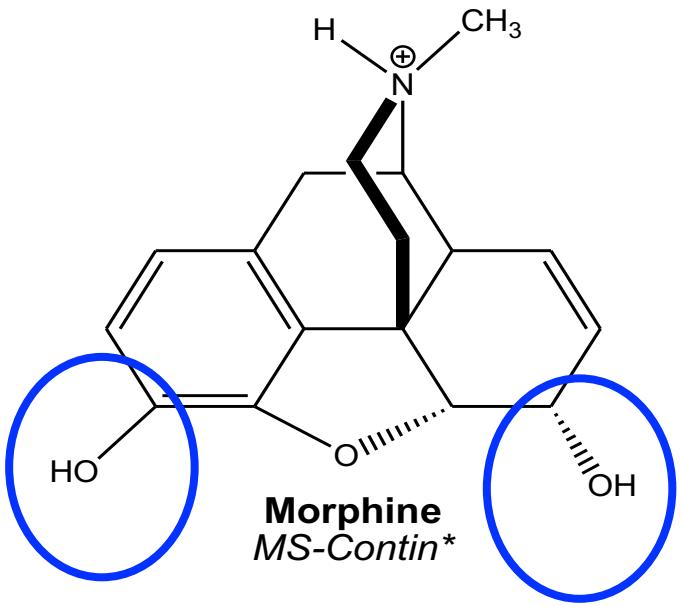
"MRS. WINSLOW'S SOOTHING SYRUP"

Should always be used when children are cutting teeth. It relieves the little sufferers at once; it produces natural, quiet sleep, by relieving the child from pain, and the little cherub awakes "as bright as a button." It is perfectly harmless, and very pleasant to taste. It soothes the child, it softens the gums, allays all pain, relieves wind, regulates the bowels, and is the best known remedy for dysentery and diarrhœa, whether arising from teething or other causes. Price 1s. 1½d. per bottle, of all chemists throughout the world. Manufactory, 493, Oxford-street, London.

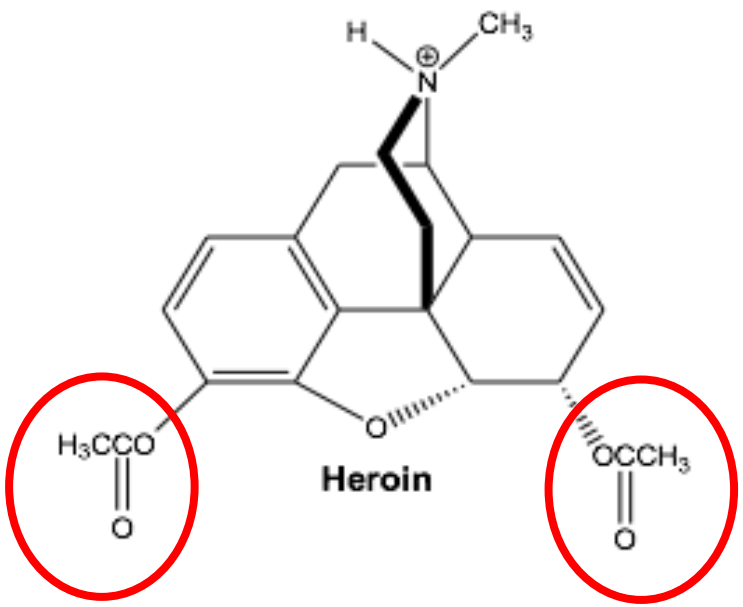
- 1849 (Maine)
- Teething syrup
- 65 mg morphine / fl oz
- 1911 "baby killer" (American Medical Association)
- 1930 (finally removed from UK market)

Historical Context

- 1874 (Germany)
  - morphine diactylated into heroin



Morphine
*MS-Contin**



Heroin

Historical Context

- 1874
  - Heroin entered US
  - Marketed to American doctors
  - “Safe, non-addictive” substitute for morphine
- 1913 Bayer stopped manufacturing
- 1924 banned in US

Historical Context

- 1952 (University of Rochester, US)
  - Morphine synthesized artificially in a lab setting
- Early 1970's
  - How opioids work in the body
  - 3 different types of opioid receptors (mu, kappa, and delta)

Laws

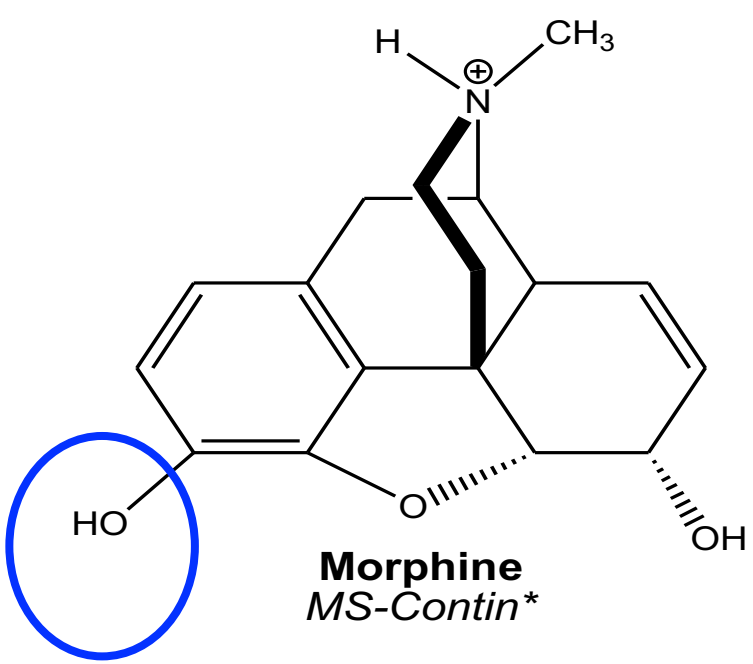
- Controlled Substance Act of 1971
- Drug Enforcement Administration
  - C-I
  - C-II *Opioids
  - C-III
  - C-IV
  - C-V
  - C-VI

Opium vs Opiate vs Opioid

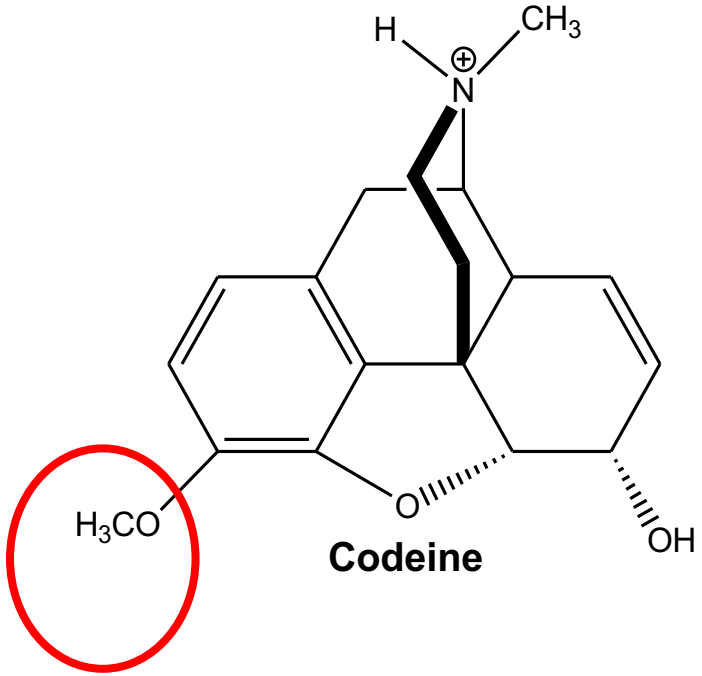
- Opium
  - Latex from the poppy plant which contains morphine
- Opiate
  - Chemical structure similar to morphine
  - Older term
- Opioid
  - Some substances act like morphine but don’t “look” like morphine’s chemical structure
  - Any drug that acts like morphine in the body
  - Chemical structure doesn’t matter

Pharmacology

- Naturally-occurring opioids



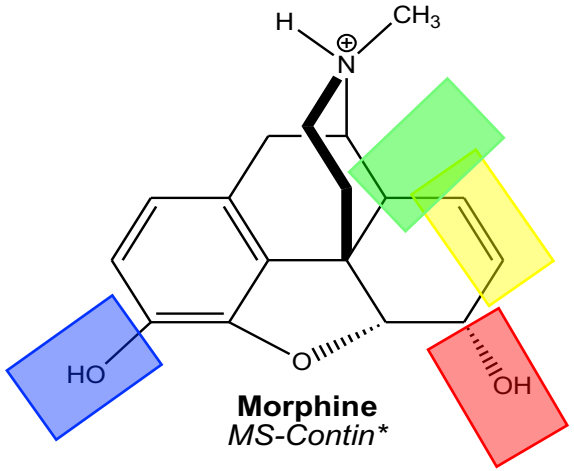
Morphine
*MS-Contin**



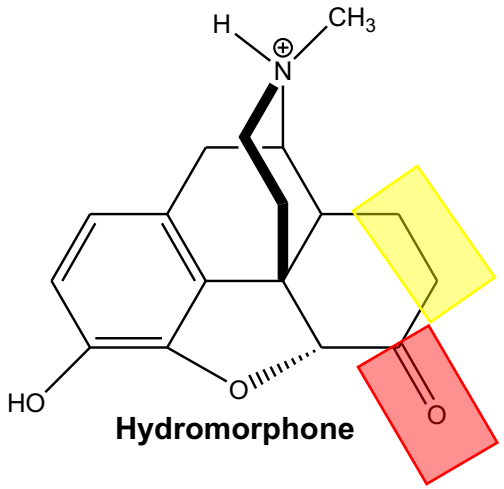
Codeine

Pharmacology

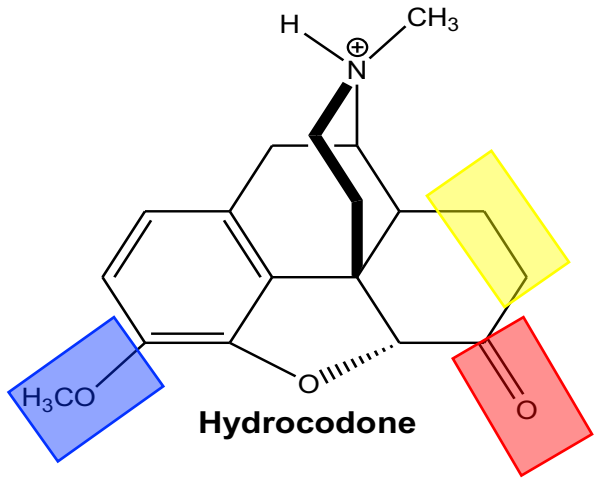
- Semisynthetic opioids



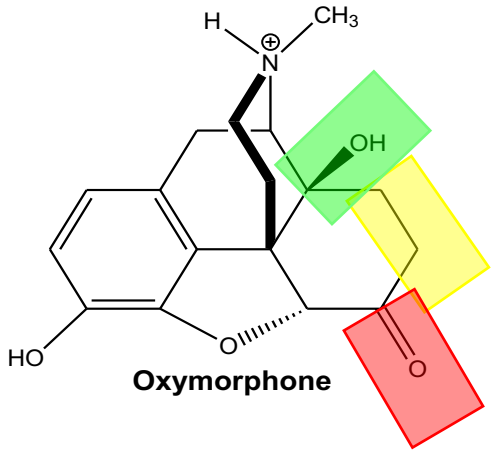
Morphine
*MS-Contin**



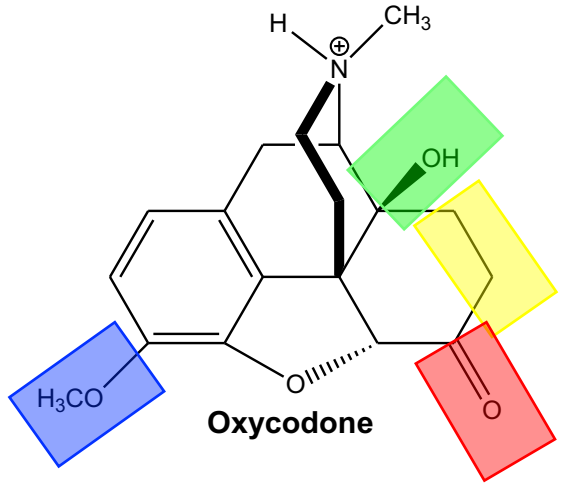
Hydromorphone



Hydrocodone



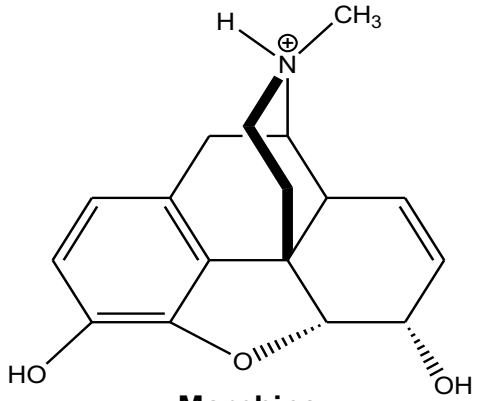
Oxymorphone



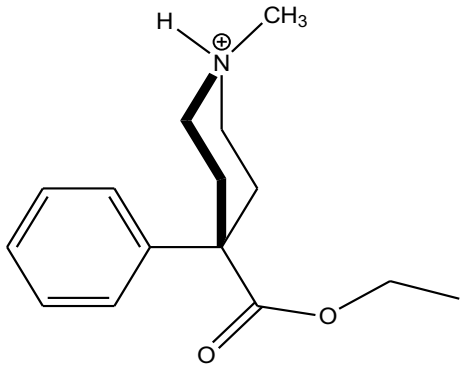
Oxycodone

Pharmacology

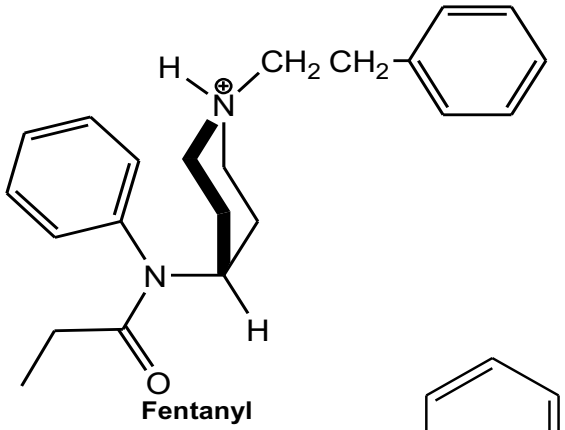
- Synthetic opioids



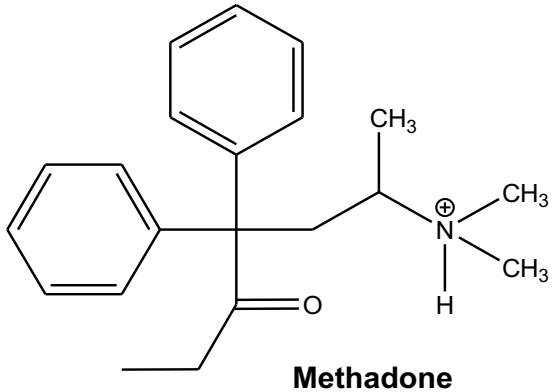
Morphine
*MS-Contin**



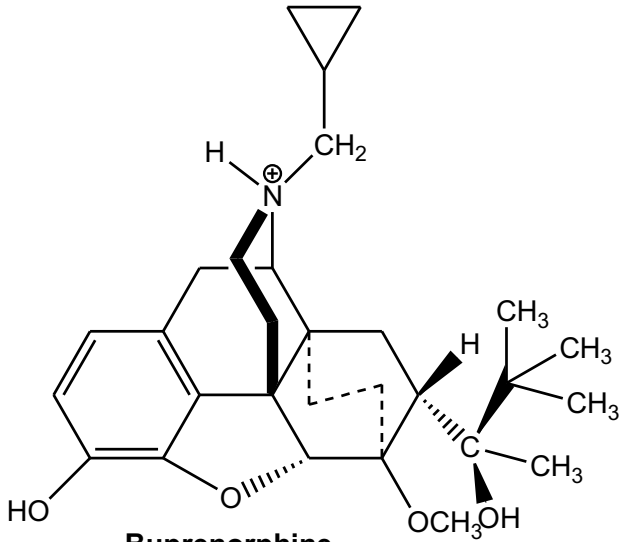
Meperidine



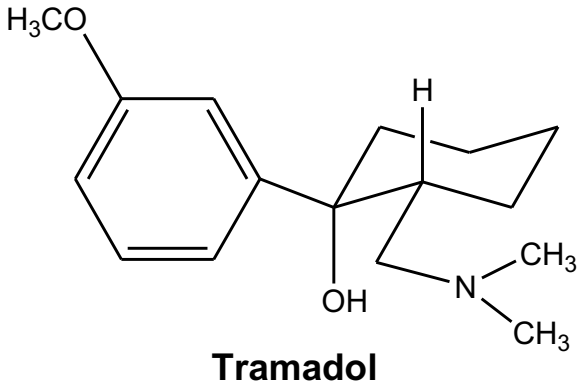
Fentanyl



Methadone

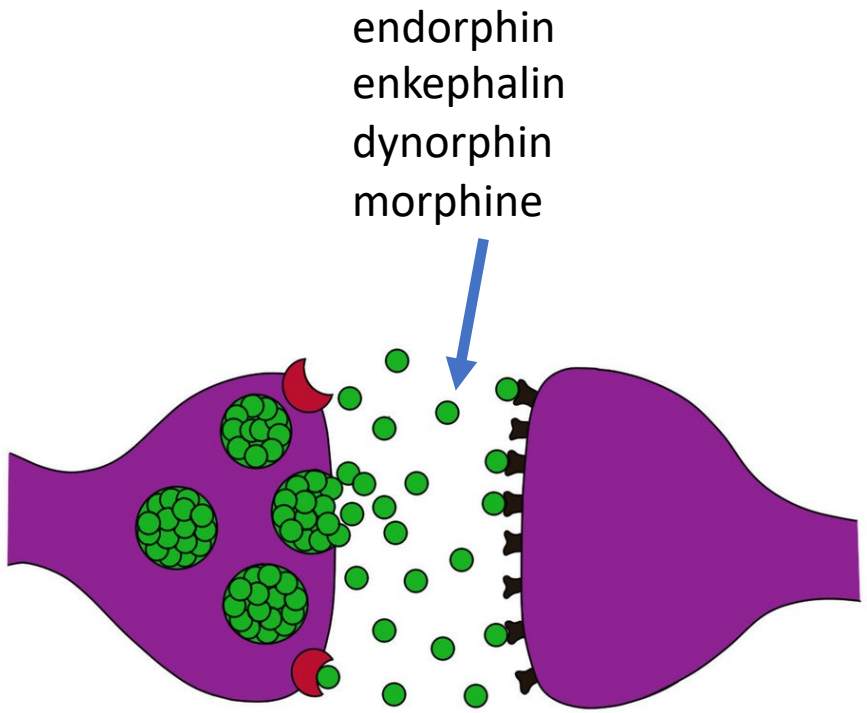


Buprenorphine



Tramadol

Pharmacology



- Opioid receptors in the body
  - On cell surfaces
  - Mu
  - Kappa
  - Delta
- Endogenous opioids (endorphins, enkephalins, dynorphins)
  - Endorphin < ***end***ogenous, ***morphin***e
- Exogenous opioids (pharmaceutical agents)

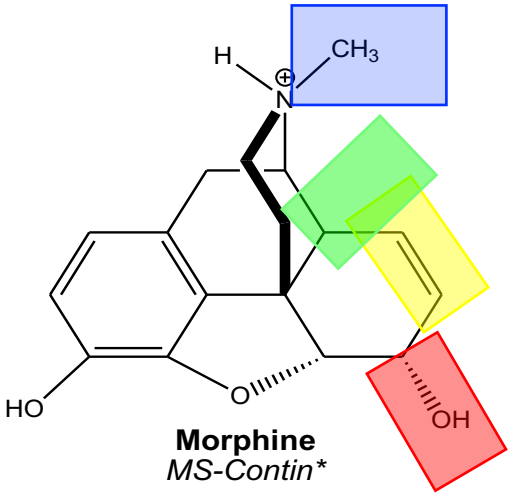
Pharmacology

Opioid Receptor Type	Action	Example
Mu	Analgesia Euphoria Constipation Respiratory Depression (*fatal*) Emesis (vomiting)	Morphine Endorphins
Kappa	Analgesia Dysphoria Sedation Miosis (pupil constriction)	Dynorphins Endorphins
Delta	Analgesia Respiratory depression	Endorphins Enkephalins

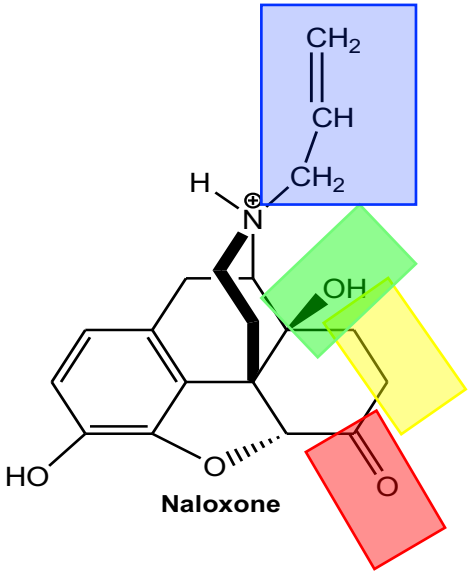
- Other Actions (non-opioid receptor activity): itching, cough suppression

Pharmacology

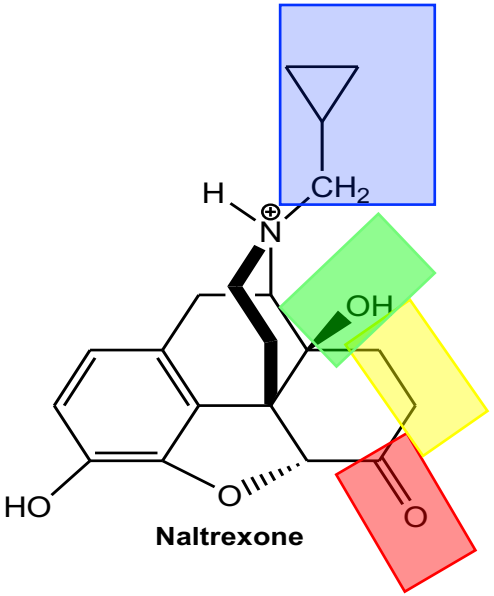
- Antidotes (reversal agents)
- Abuse-deterrrant formulations



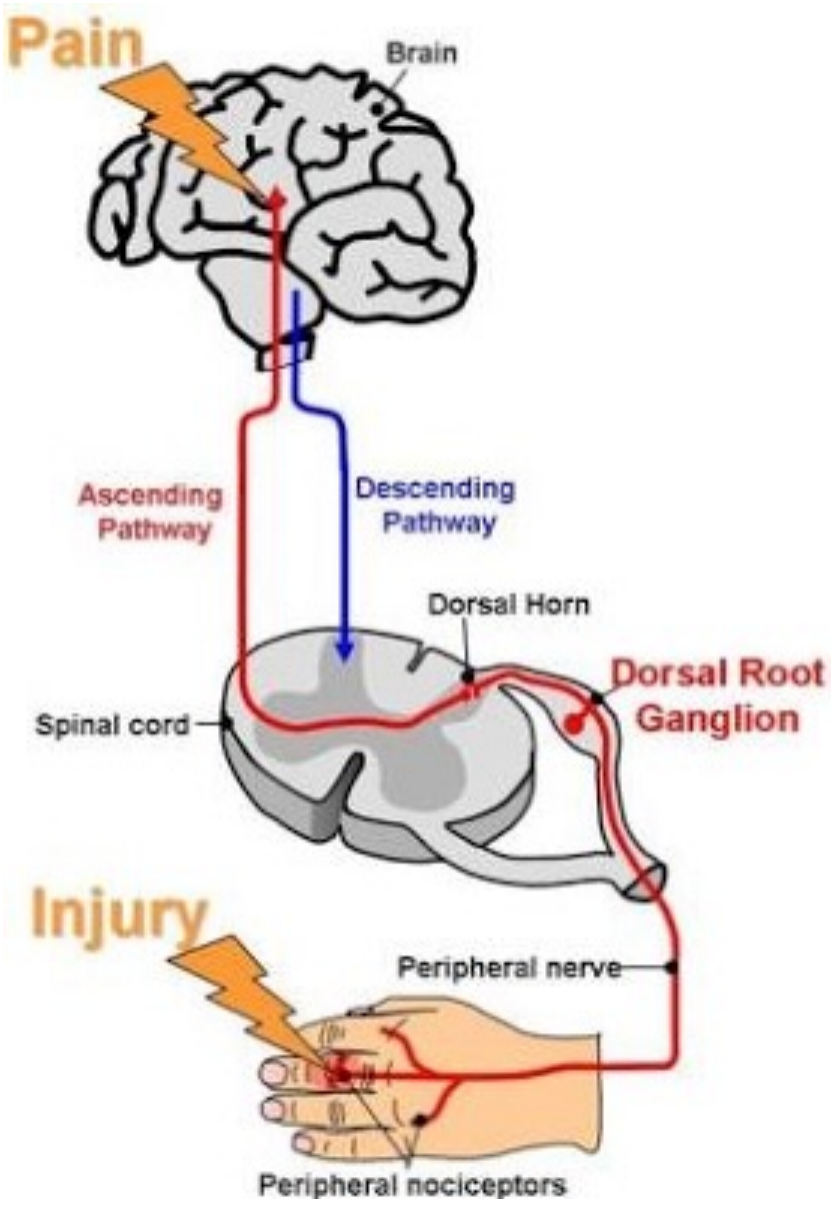
Morphine
*MS-Contin**



Naloxone



Naltrexone



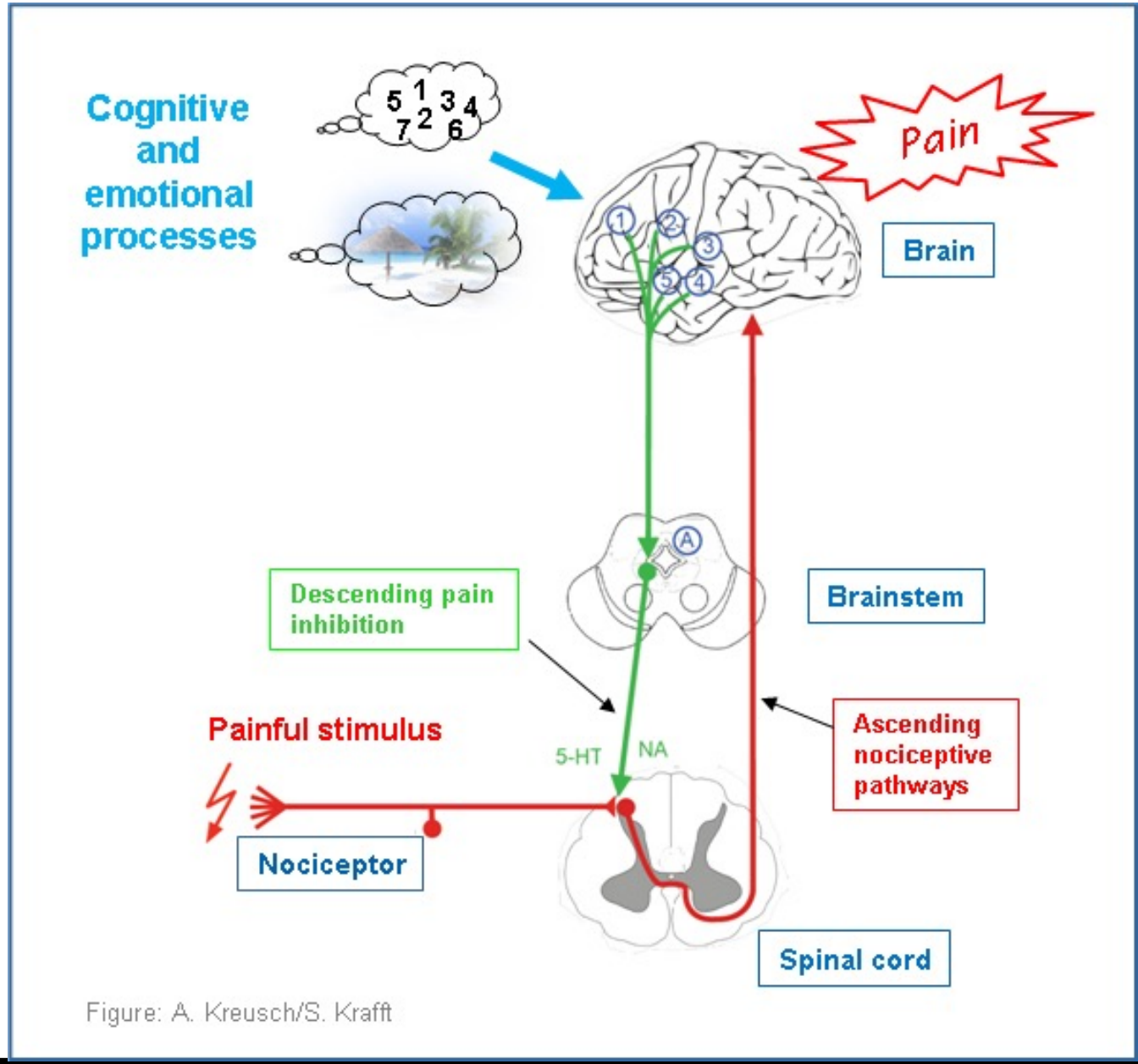
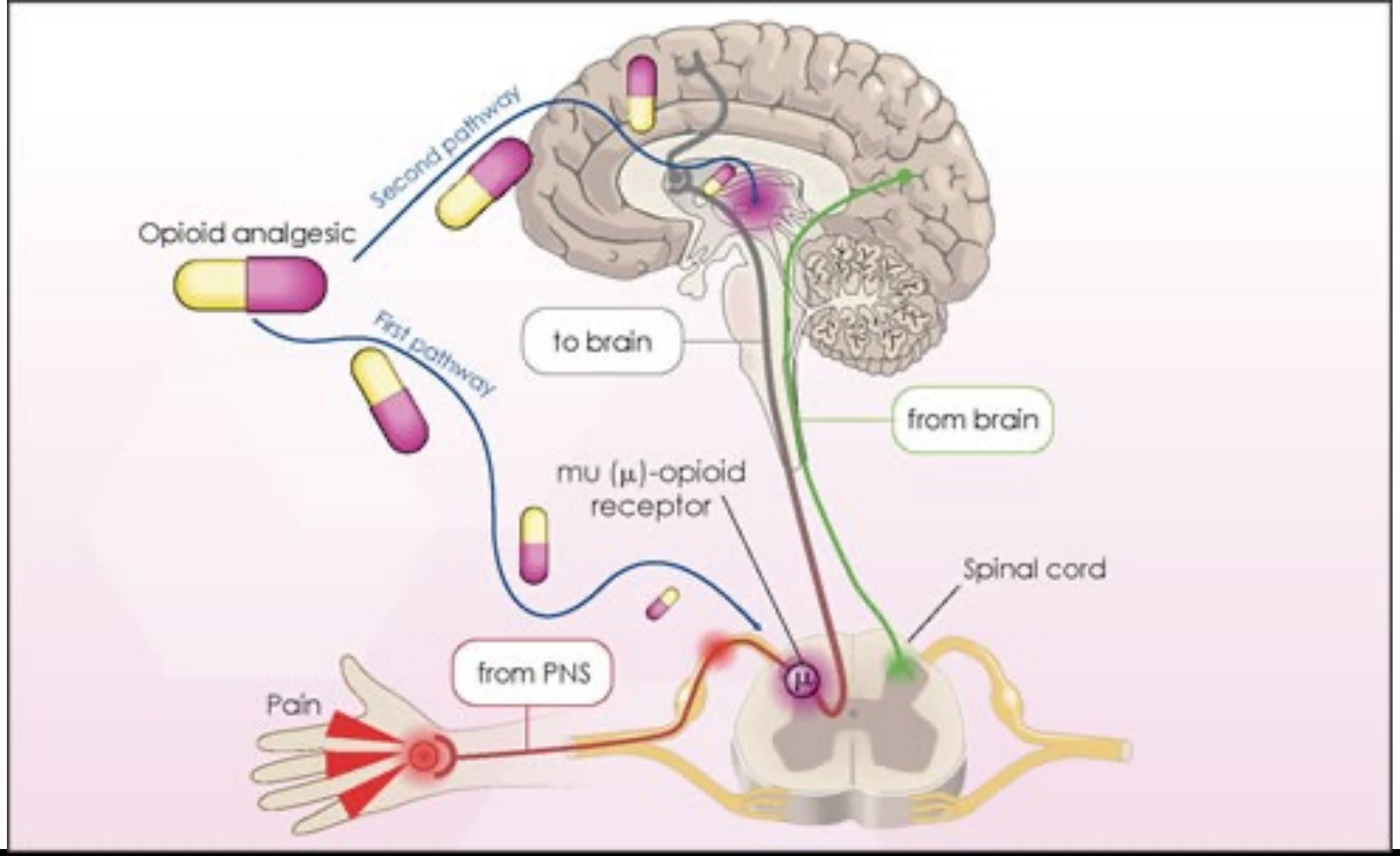
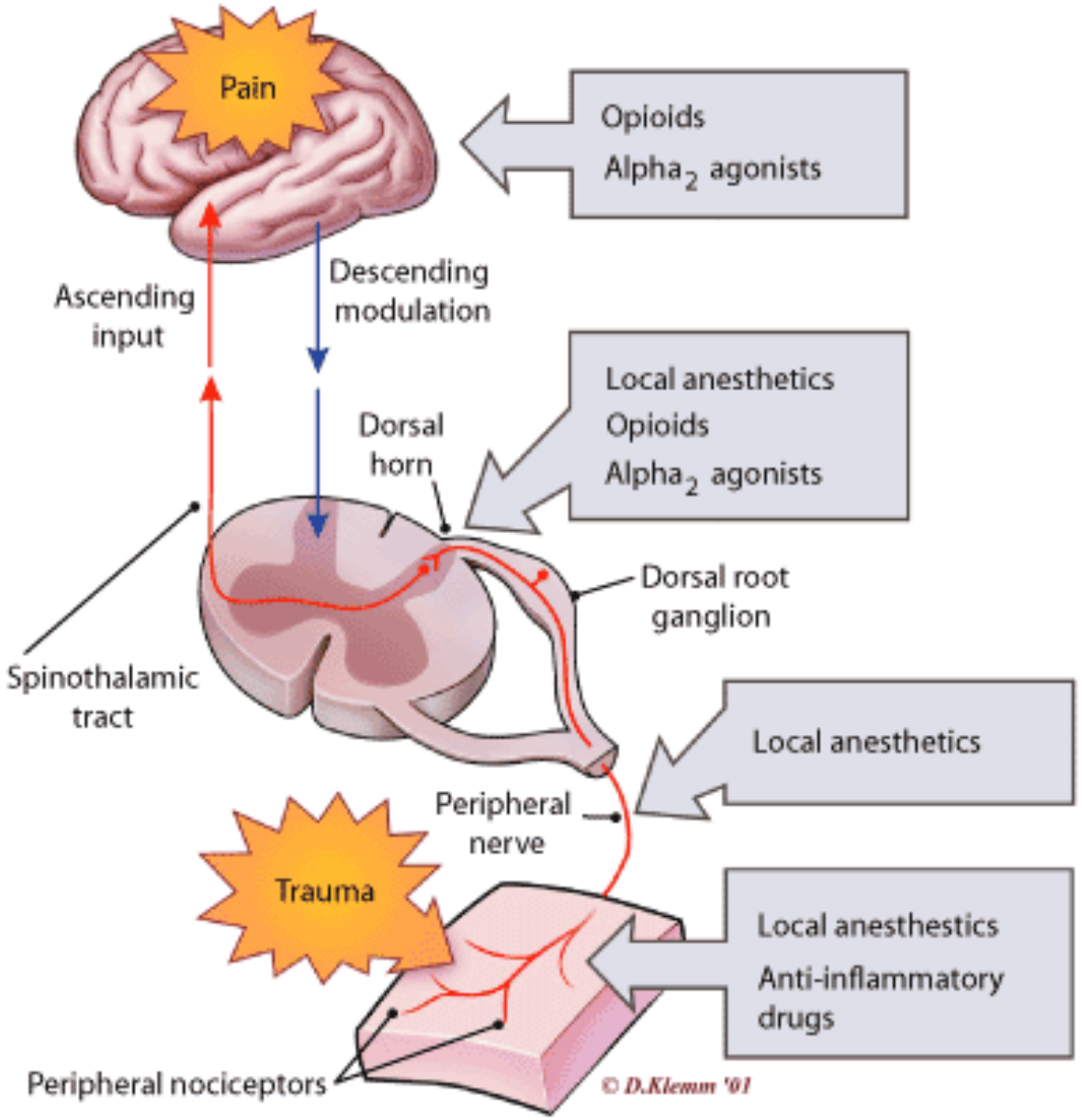


Figure: A. Kreusch/S. Krafft

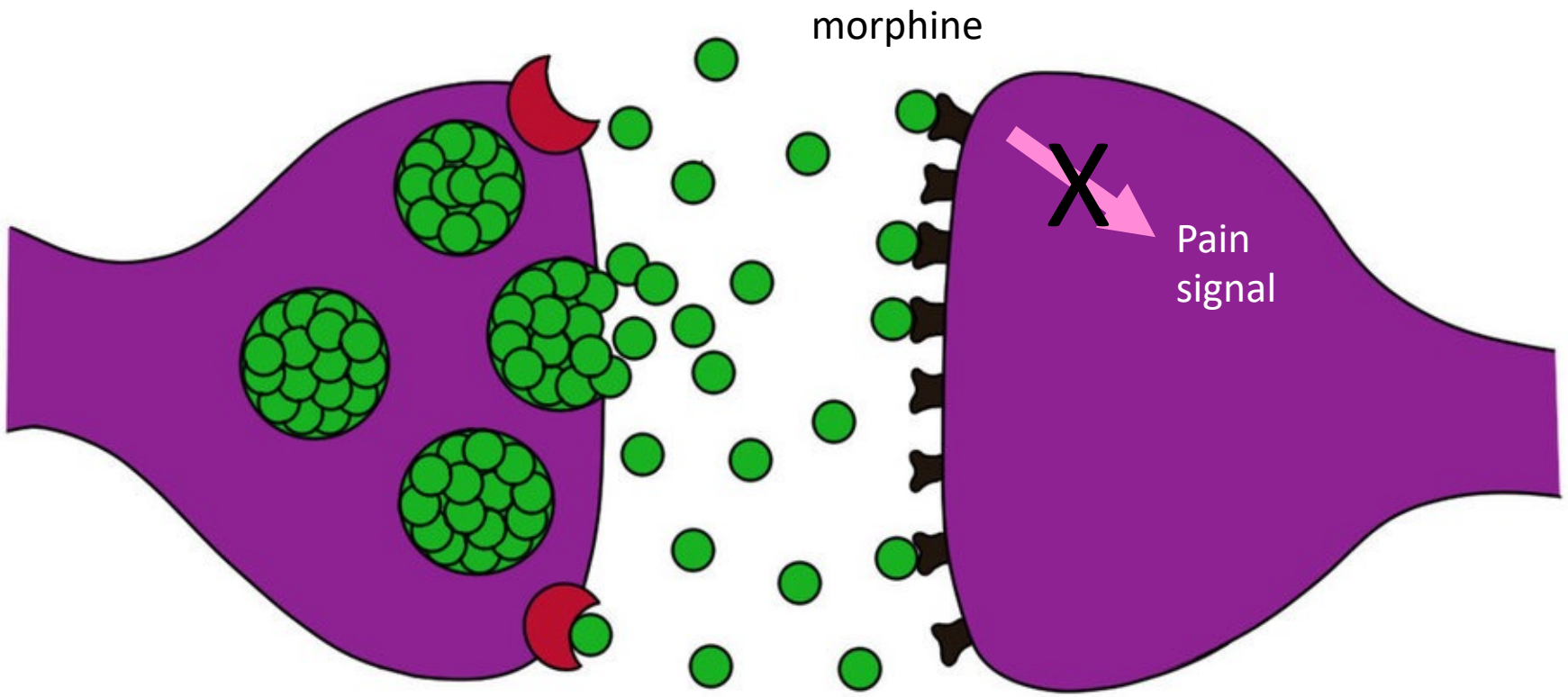

Second pathway
Opioid analgesic
First pathway
to brain
from brain
mu (μ)-opioid receptor
Spinal cord
from PNS
Pain


Pain
Opioids
Alpha$_2$ agonists
Ascending input
Descending modulation
Local anesthetics
Opioids
Alpha$_2$ agonists
Dorsal horn
Dorsal root ganglion
Spinothalamic tract
Local anesthetics
Peripheral nerve
Trauma
Local anesthestics
Anti-inflammatory drugs
Peripheral nociceptors
© D.Klemm '01

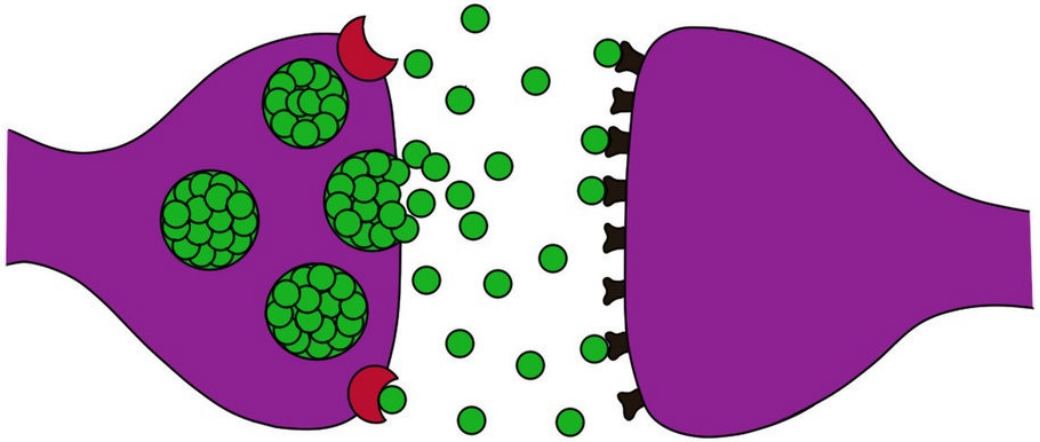
Effects of Opioids

- Analgesia (centrally-acting; as opposed to local)
- Cough suppression (antitussive)
- Respiratory depression (rate and volume) **
- Decreased GI motility (constipation)
- Drowsiness
- Pinpoint pupils (miosis)
- Itching (histamine release)
- Convulsions
- Emesis

Pharmacology



Theory of Addiction



- Dopamine
  - Reward
  - Euphoria
- Cocaine inhibits reuptake (DA stays around longer)
- Opioids
  - Mu Opioids → inhibit neurons that inhibit DA release → DA is released without inhibition
  - Kappa Opioids → inhibit DA release; DA release decreases → feeling of dysphoria

Drugs of Abuse

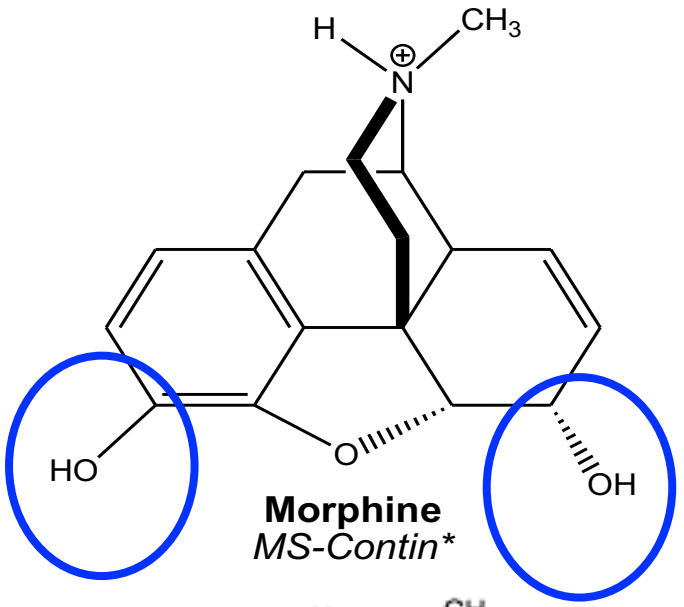
- Use of a drug in a way that is not medically approved

Addiction Potential of Selected Drugs

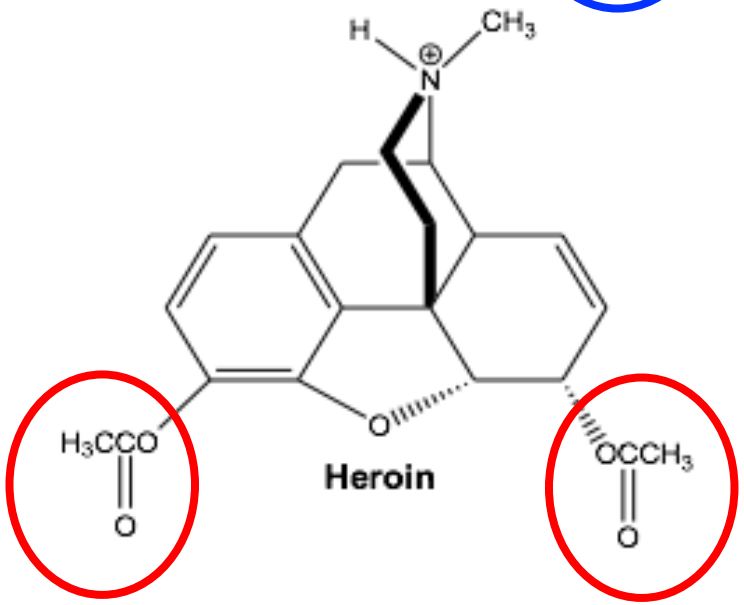
Drug	Addiction Potential (1=addictive; 5=highly addictive)
Ketamine	1
LSD, mescaline	1
Cannabinoids (marijuana)	2
Alcohol	3
Benzodiazepines	3
Opioids	4
Nicotine	4
Amphetamines	5
Cocaine	5

Heroin

- 3,6-diacetyl morphine
  - Crosses the blood-brain barrier more readily than morphine
  - Enzymes in brain tissue rapidly cleave one of the acetyl groups
  - 6-acetyl morphine has mu opioid activity in excess of morphine → intense euphoric rush



Morphine
*MS-Contin**



Heroin

Drug Tolerance

- Escalation of dose to maintain effect
- Pharmacokinetic tolerance
  - Person's body becomes more efficient at metabolizing (clearing) the drug over time
  - Higher doses are needed
- Pharmacodynamic tolerance
  - Person's opioid receptors actually change with repeated exposure
  - Cell's adaptive mechanism to protect itself from overstimulation
  - Ex: downregulation of opioid receptors
- Opioid Tolerant
  - ≥ 60mg oral morphine daily x ≥1 week
  - (opioid equivalent)

Withdrawal

- Cell's adaptive changes become fully apparent once drug exposure is terminated
- Lasts several days
- Intense dysphoria
- Nausea / vomiting / diarrhea
- Muscle aches
- Lacrimation (eyes tearing)
- Rhinorrhea (nose running)
- Mydriasis (dilated pupils)
- Fever / Chills / goosebumps
- Sweating
- Yawning

Dependence

- Physiological response
- Invariably occurs with repeated exposure to certain drugs
  - Opioids
  - Beta Blockers
  - Vasoconstrictors
- Manifested as withdrawal symptoms upon abrupt discontinuation
- After withdrawal is over, drug is no longer desired

Addiction

- Behavioral response (mal-adaptive)
- Compulsive desire and use of drug despite negative consequences, even after withdrawal has ended
- “Wanting without liking”
- Some drugs of abuse do not lead to addiction
  - Ketamine / hallucinogens alter perceptions w/o affecting the dopamine system

Treatment of Opioid Addiction

- Long-acting opioid (methadone or buprenorphine)
  - Prevents withdrawal
  - Longer activing: mechanisms in reward system have time to adapt and attenuate intense euphoric rush
  - Blocks morphine or heroin from binding at those same receptors
- A patient on methadone remains opioid-dependent
  - Controversial
- Switzerland, Netherlands
  - Supervised injection of heroin as replacement therapy
- Methadone is also used to treat cancer pain
  - Indication is extremely important for legality of dispensing

Abuse-deterrent formulations

- Naloxone or Naltrexone
- If crushed and injected, precipitates rapid withdrawal

Adverse Effects of Opioids

Major Adverse Effects of Opioid Analgesics	Manifestation
Mood Changes	Dysphoria, Euphoria
Somnolence	Sedation, inability to concentrate
Stimulation of chemoreceptor trigger zone	Nausea, vomiting
Respiratory depression	Decreased respiratory rate
Decreased GI motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention
Histamine release	Urticaria, pruritus Exacerbation of asthma (rare)
Tolerance	Larger doses needed for same effect
Dependence	Withdrawal symptoms upon abrupt discontinuation

Morphine milligram equivalents (mme)

Opioid	Equipotent Dose (PO)	Equipotent Dose (IV)
Morphine	30mg	10mg
Codeine	200mg	120mg
Fentanyl	(transdermal patches) 1mcg/hr/patch = 2mg PO morphine / day 25mcg/hr/patch = 60mg PO morphine / day	0.1-0.2
Hydrocodone	5-10mg	---
Hydromorphone	7.5mg	1.5mg
Methadone	20mg	10mg
Oxycodone	10-30mg	---
Oxymorphone	10mg	1mg
Tramadol	200mg	---
Buprenorphine	---	0.3 (0.4 for SL)

Morphine milligram equivalents (mme)

Calculating morphine milligram equivalents (MME)

OPIOID (doses in mg/day except where noted)	**CONVERSION FACTOR**
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Assigned Articles

- Abuse of prescription opioids often leads to heroin use
- Both can result in potentially fatal overdoses (respiratory depression)
- Many parties (including state governments) want to hold drug companies liable for unscrupulous promotion of opioids without full disclosure of their addictive nature

Discussion Questions

- What was the main task Birnbaum et al. (2011) and Florence et al. (2016) set out to do?
- What conclusions did they reach?

Discussion Questions

- What 3 categories of costing did the two articles utilize to calculate societal costs of prescription opioid abuse in the United States?
- What costs were ignored?
- What about ICD-9 coding confounds their results?
- Where did the authors obtain their data?
- In what ways could their calculations be considered problematic?
- What were some strengths of the articles?
- What were some weaknesses of the articles?

Conclusions

- What conclusions should we make from these two articles?

Back-up

Pharmacology