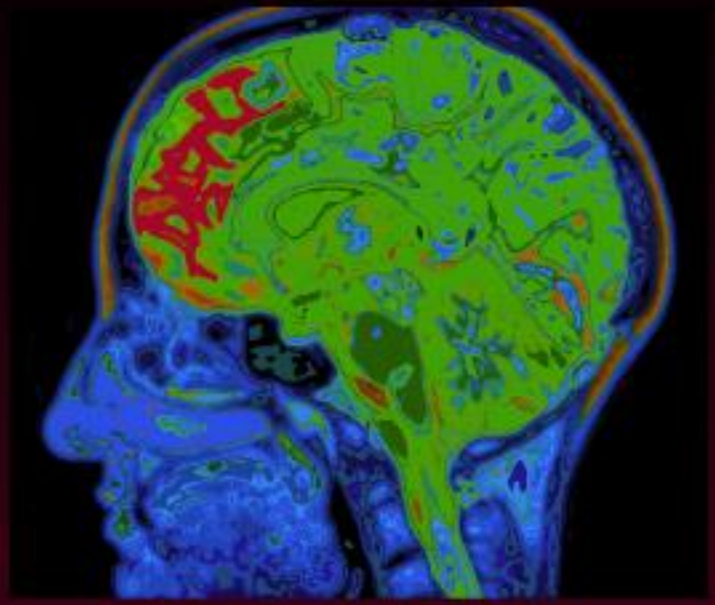

Brain science of addiction

January 22, 2022

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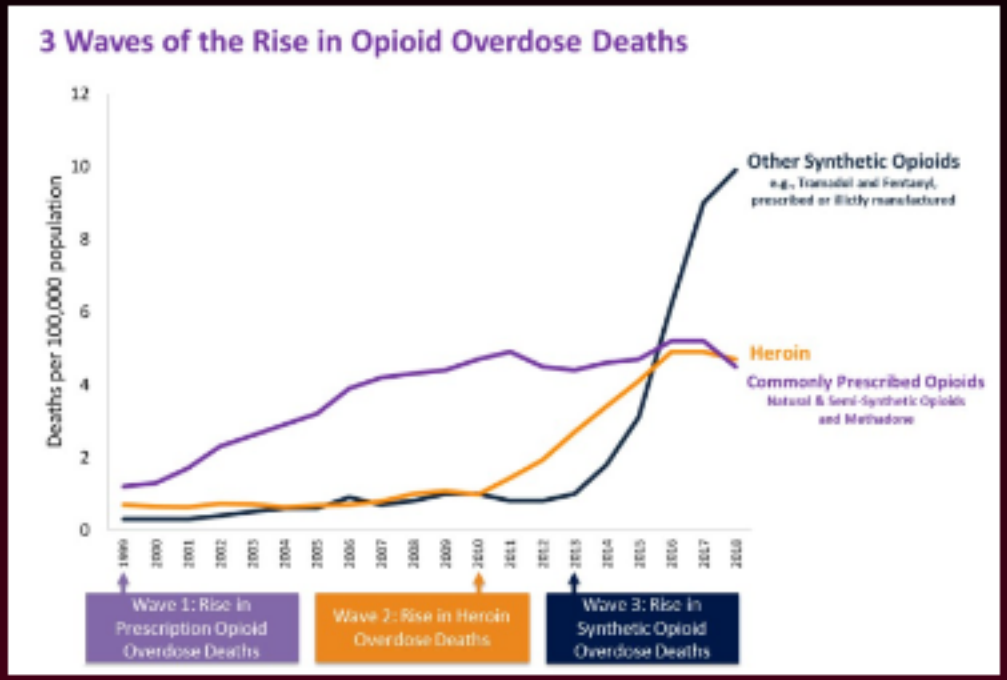
Outline of presentation

- Opioids and the epidemic
- Effects of opioids on the nervous system
- Opioid maintenance therapies
- Addiction as a brain disease
- Future avenues

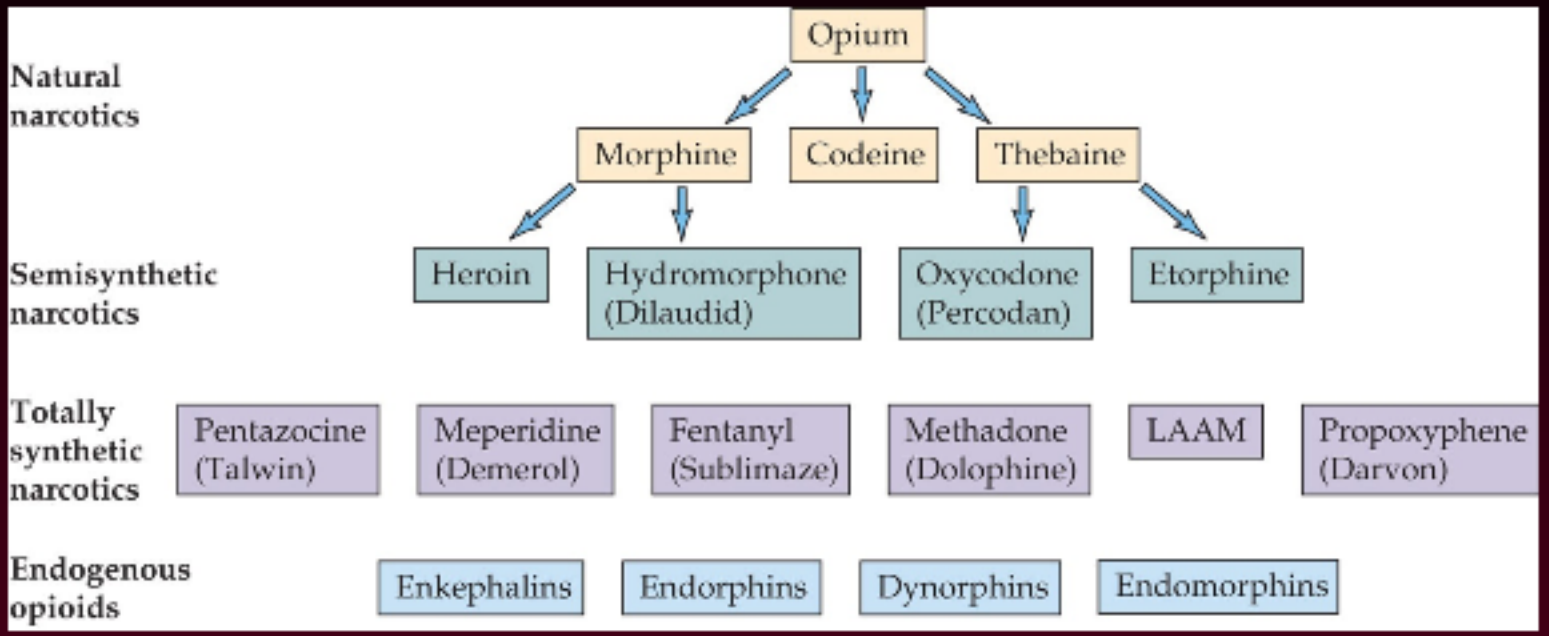
The opioid epidemic



Three general “waves”:

1) over-prescription / over-marketing of prescription opioids
2) restrictions on amounts of opioids dispensed; patients seek opioids more frequently and turn to widely available low cost heroin
3) infiltration of the drug market with highly potent synthetic opioid receptor agonists such as fentanyl and its derivatives

Opioid terminology



- **opioids** - umbrella term for **all chemicals** acting at opioid receptors
- **opiates** - term for natural and semi-synthetic chemicals derived from the opium poppy (also referred to as narcotics, though this term tends to be associated with other illicit drugs such as cocaine)
- **endogenous opioids** – natural chemical messengers in the brain such as endorphins

The opium harvest

Papaver somniferum




- opium poppies nicked by hand with a blade, allowed to ooze raw opium latex for several days
- latex collected by hand
- morphine concentrated and acetylated to heroin (diacetylmorphine, diamorphine)



Former opioid products

LAUDANUM.

(Tinct. Opium.)

U. S. P. Strength. Directions on each bottle for old and young.

No. D1581 1 oz. bottle, 10c; per doz. $1.10
2 oz. bottle, 18c; per doz. 2.00
4 oz. bottle, 28c; per doz. 3.00

PAREGORIC.

ALWAYS USEFUL.

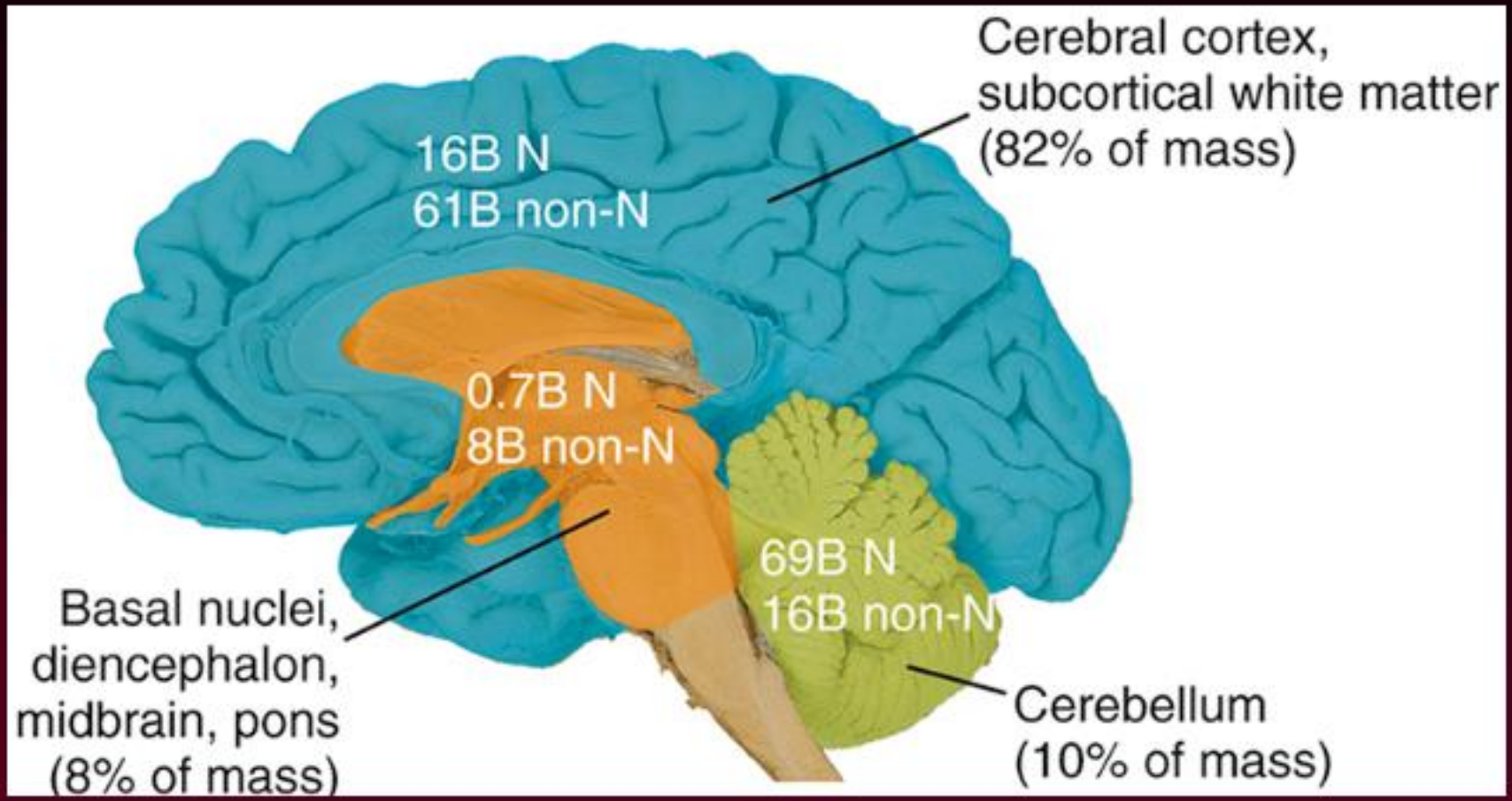
BOTH FOR CHILDREN AND ADULTS.

Full directions.

No. D1582 2 oz. bottle, 12c; per doz. $1.25
4 oz. bottle, 18c; per doz. 1.75

- 1800's – tinctures of opium sold over-the-counter
  - laudanum: ~10% dried opium powder dissolved in 20-50% alcohol
  - paregoric: ~0.4% morphine in 45% alcohol
- 1898-1920 - Heroin used as cough suppressant

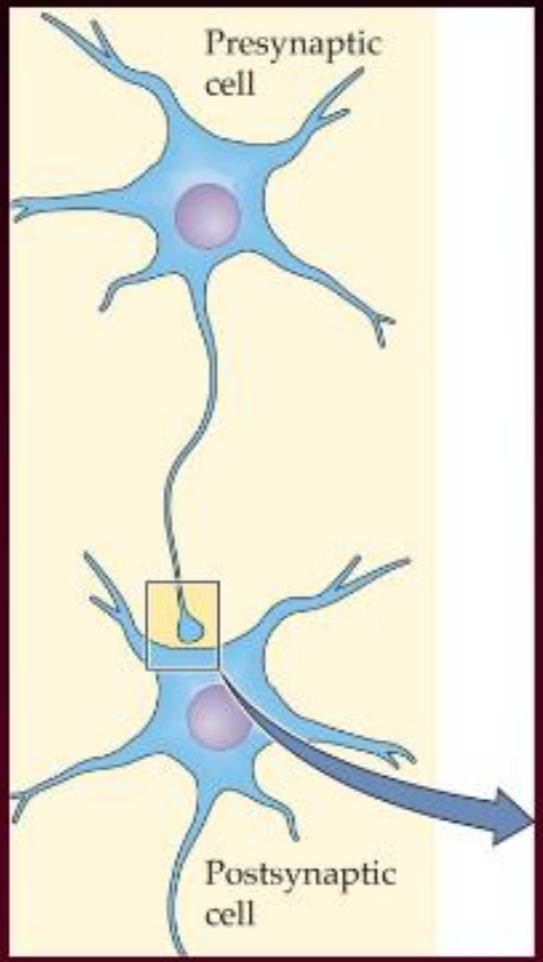
The human brain



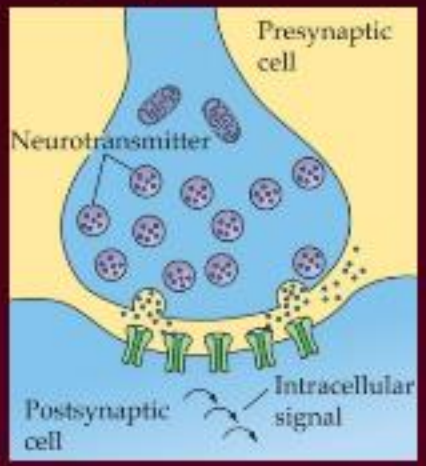
Neuronal communication (chemical synaptic transmission)

receiving zone

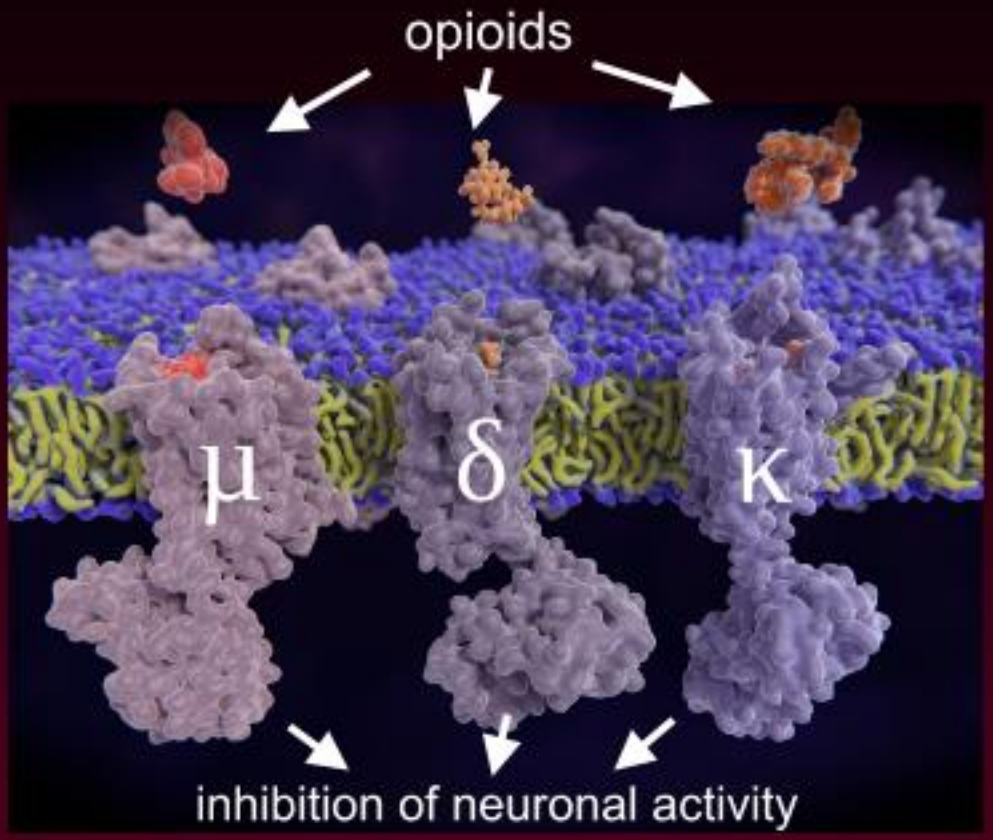
transmitting zone



- neurotransmitters are chemical messengers secreted by neurons
- range in size from two atoms (nitric oxide) to chains of 20-50 amino acids (endorphins) to larger proteins



Opioid receptors



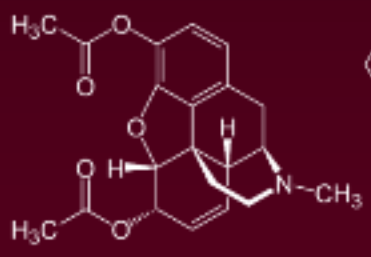
- opioid drugs bind to μ, δ, and/or κ receptors, which serve as receptors for endogenous opioids such as endorphins
- abused opioids (morphine, fentanyl, hydrocodone, oxycodone, etc.) act as agonists (activators) primarily at μ receptors

Fentanyls

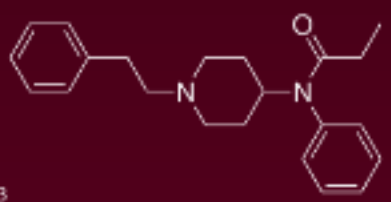
highly potent μ receptor agonists

Lethal doses for average adult

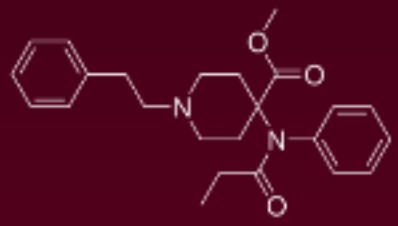
heroin
10-12 mg



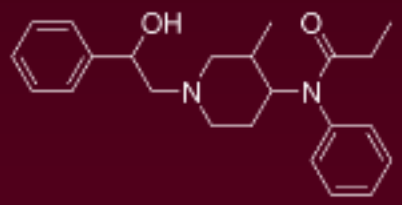
fentanyl
1-2 mg



carfentanil
0.02 mg

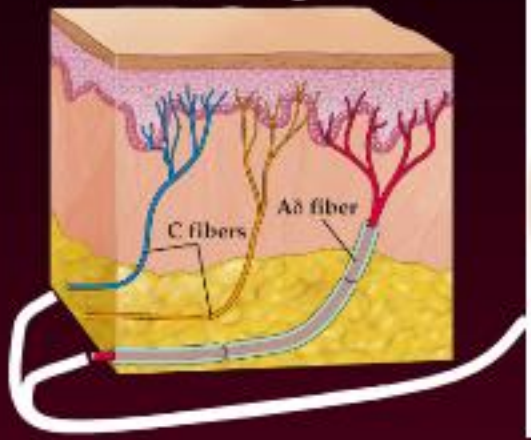


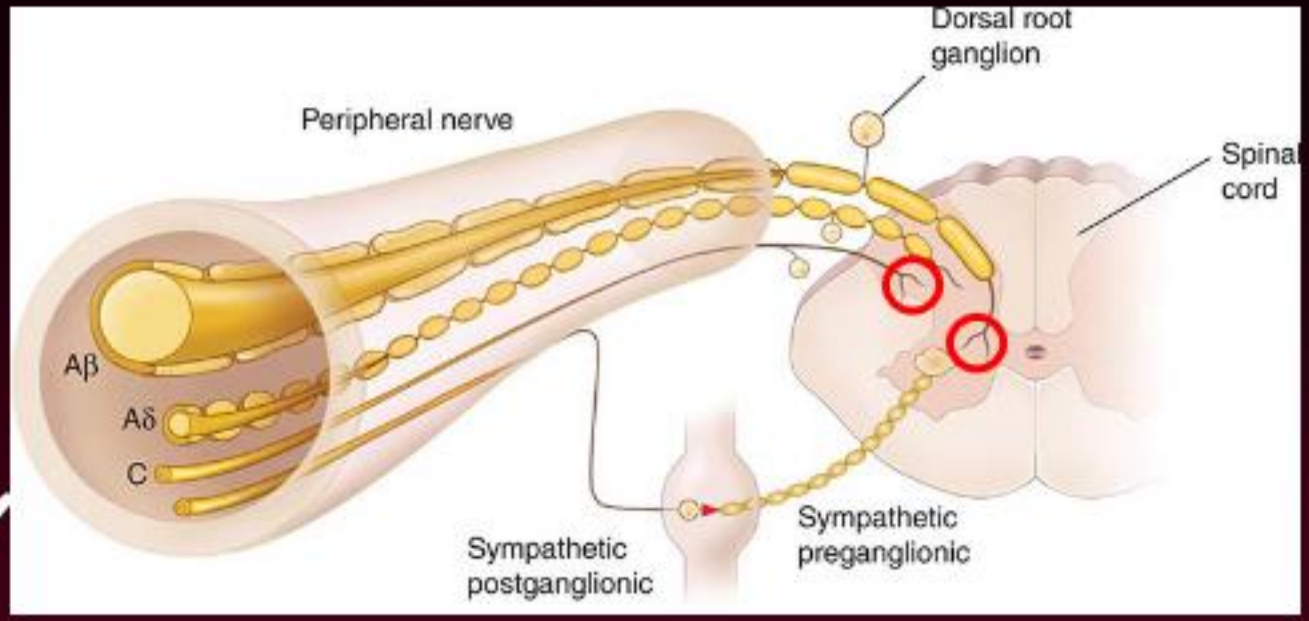
hydroxymethyl-
fentanyl <0.01 mg



Anatomy of pain

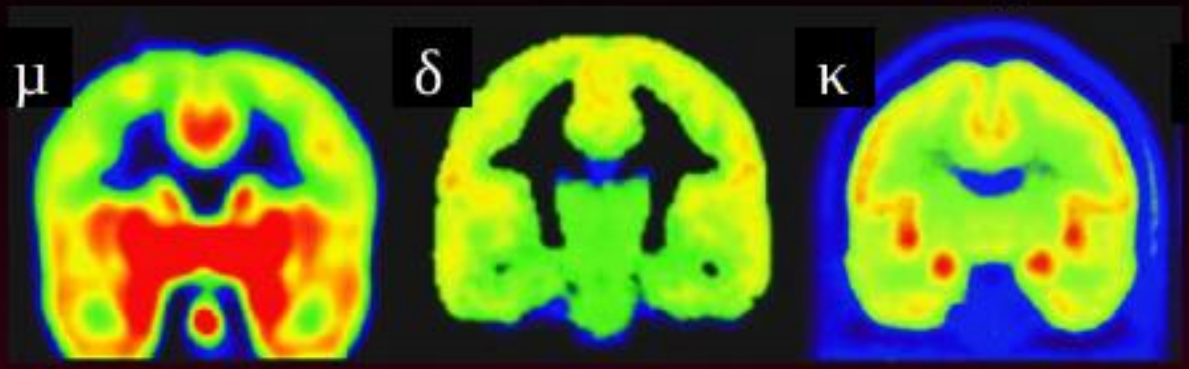
peripheral nerve endings

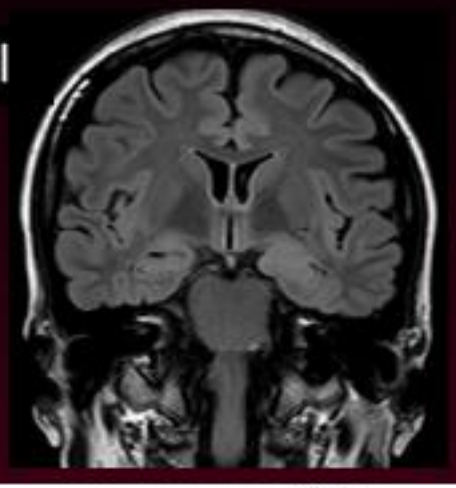




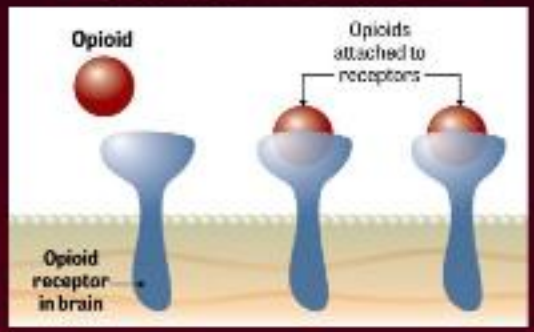
- sensory information carried by neurons (peripheral nerves) to spinal cord
- enter spinal cord via the dorsal horn
- Aδ and C fibers specifically carry pain sensations
- Aβ and other fibers carry convey normal touch and pressure signals
- opioid receptors are located on only on Aδ and C fibers entering the spinal cord, thus opioids selectively inhibit pain sensations

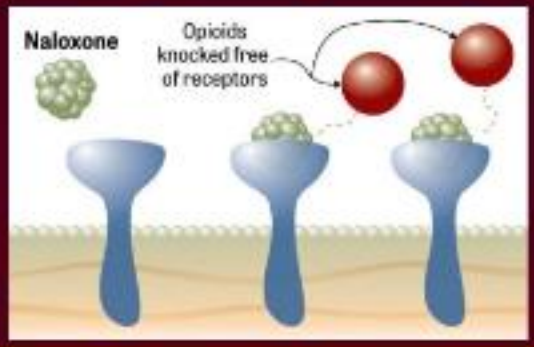
Distribution of brain opioid receptors





- μ opioid receptors have one of the highest levels of expression in the brain, including **reward centers** (addiction and motivation) and the **brainstem** (respiratory control)
- naloxone (Narcan) - broad spectrum opioid receptor **antagonist** (blocker) that displaces opioid drugs from their receptors





Treatment strategies

withdrawal management medications

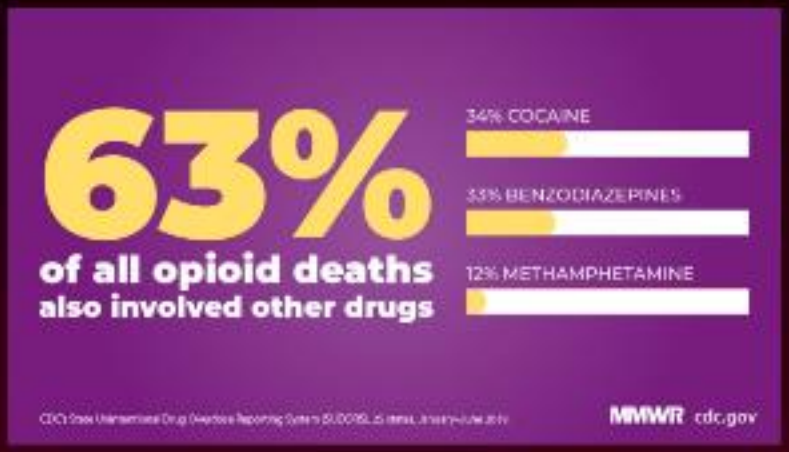
Maintenance assisted therapies (MATs)

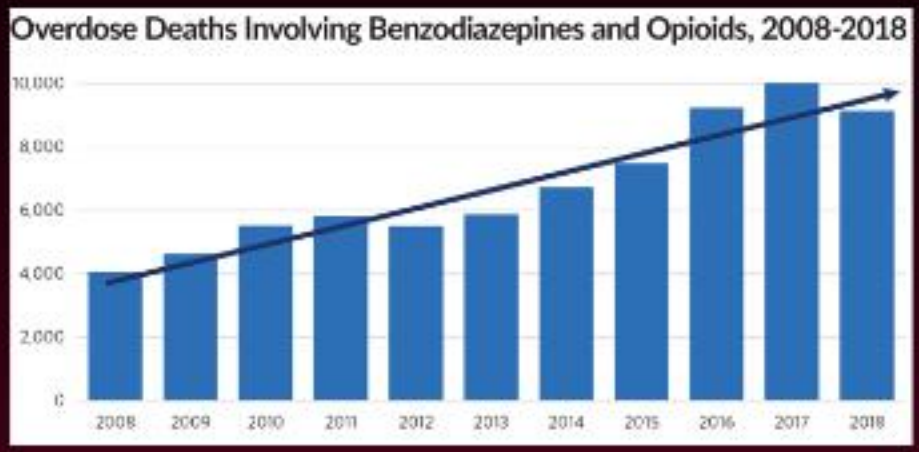
- long-acting μ receptor agonist
- long but variable elimination half-life (10-60 hr)

- partial μ receptor agonist
- Suboxone – abuse deterrent formulation

- unregulated μ receptor agonists
- efficacy not yet established

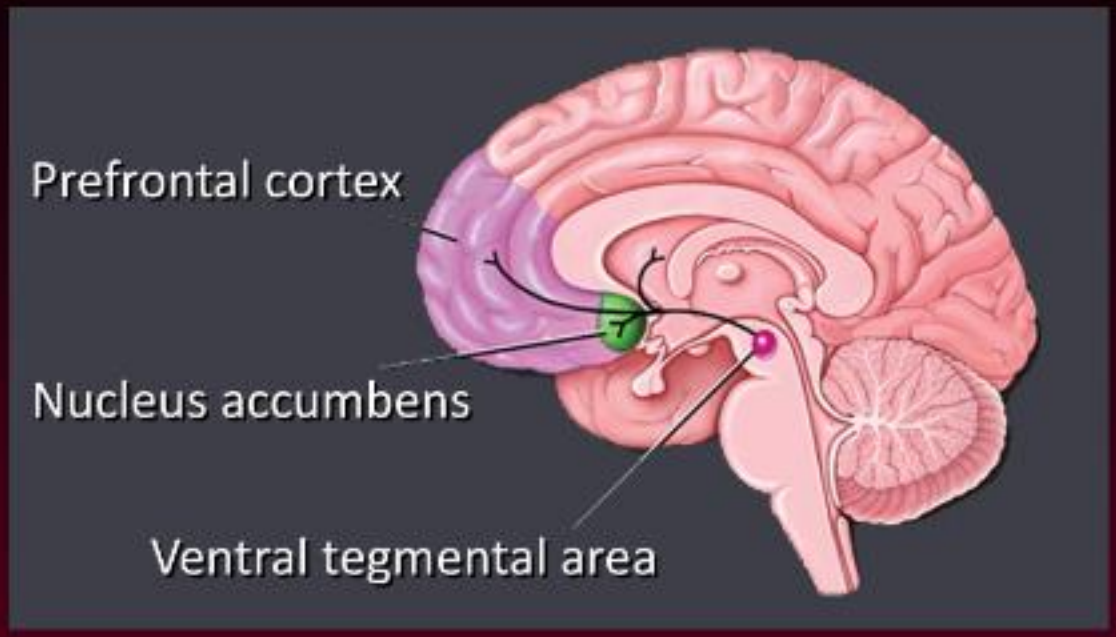
Opioids and polysubstance abuse





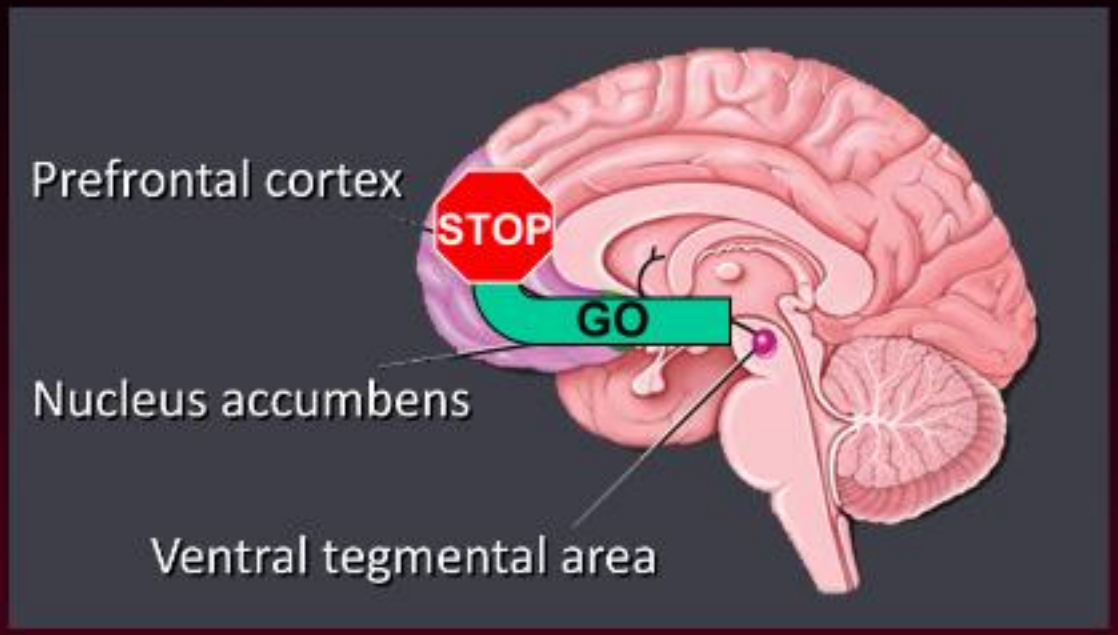
- multiple drugs are often used with opioids
- alcohol and **benzodiazepines** (i.e., Xanax, Ativan, Valium) are often to self-medicate symptoms of withdrawal
- **stimulants** such as cocaine and methamphetamine used to counteract opioid-induced sedation
- all increase the risk adverse events and overdose

Dopamine theory of addiction



- primary reward or "pleasure" system of brain consists of **mesolimbic dopamine system** (midbrain connections to forebrain)
- activated by both drug and natural rewards (food, love, music, etc.)
- abused drugs activate this system to greater degree than natural rewards, 'hijacking' the system to favor drug rewards

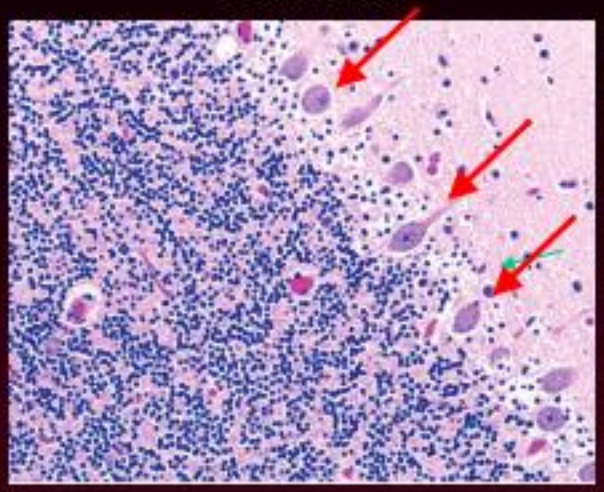
Hypofrontality theory of addiction



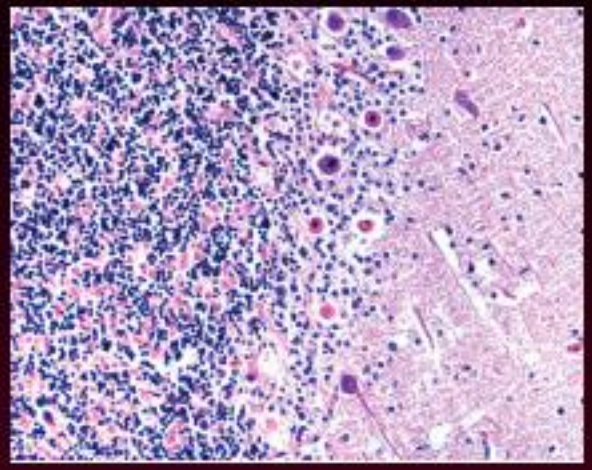
- pleasurable or novel experiences driven by mesolimbic system ("go" circuit)
- prefrontal cortex (PFC) exerts executive control over the "go" system, serves as a "stop" signal to provide impulse control, proper decision-making, and appropriate responses to external cues and punishment
- PFC is last brain region to fully mature
- hypofrontality theory asserts that abused drugs cause deficits in PFC structure and function, leading to impaired impulse control, poor decision-making, and compulsive drug use despite adverse consequences

Disease theory of addiction

Normal



Opioid abuser



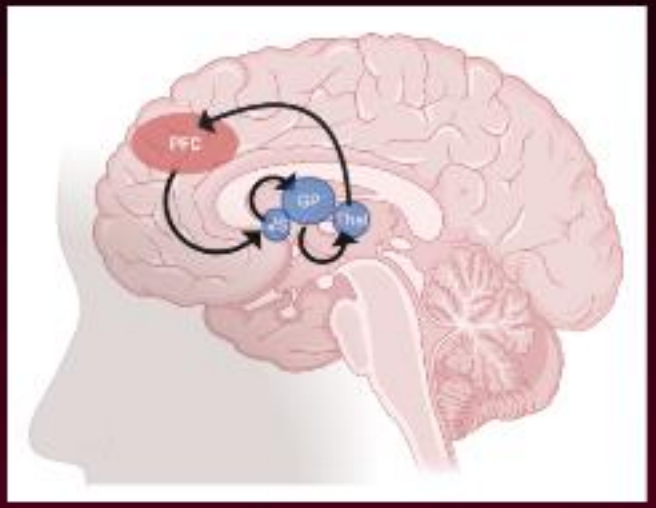
- Merriam-Webster dictionary defines a disease as a "*a condition of the living animal or plant body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms*"
- brain disease concept largely attributed to Dr. Alan Leshner (then director of National Institute on Drug Abuse) - *"addiction is tied to changes in brain structure and function is what makes it, fundamentally, a brain disease"*
- concept has gained increasing acceptance, and challenges the long-held view that addiction is a character flaw or moral weakness
- helped destigmatize addiction and increase treatment accessibility

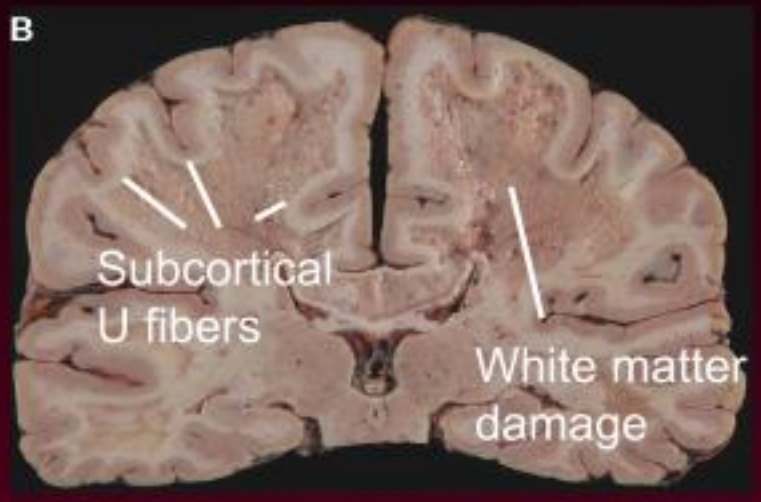
Brain changes in opioid addiction

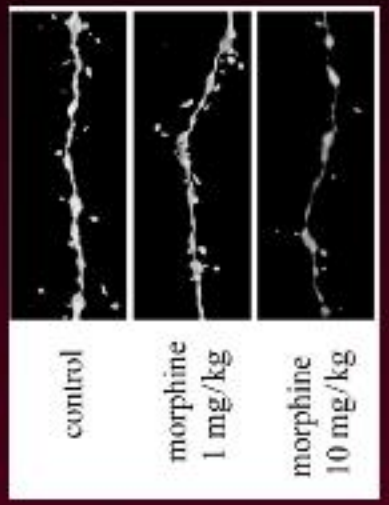
The molecular neurobiology and neuropathology of opioid use disorder

Christopher A. Blackwood **, Jean Lud Cadet *

Current Research in Neurobiology 2 (2021) 100023







- oxycodone – reduced functional connectivity between PFC and limbic (emotion) circuits
- heroin – reduced cortical gray matter, reduced mesolimbic region volume, toxic leukoencephalopathy
- fentanyl, methadone – cerebral swelling (edema)
- morphine – alterations of fine neuronal structure (animal studies)

Arguments against (or for revision of) the disease theory

frontiers in PSYCHIATRY
Addiction and the brain-disease fallacy
March 2014 | Volume 4 | Article 141 | 1

- absolves personal accountability
- some patients can abstain and recover without medical treatment (i.e., Vietnam veteran study)
- minimizes psychosocial and environmental influences
- biases treatment efforts towards medicalized vs. psychosocial approaches
- underemphasizes need to understand how the brain *recovers* from addiction, not just how it becomes addicted

Considerations for future research

- opioid analgesics with minimal abuse liability
- non-opioid-based maintenance therapies
- identification of at-risk populations (gene x environment interactions)
- non-invasive neuromodulatory approaches
- other experimental treatments?