Brain science of addiction
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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

- 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

Cerebral cortex, subcortical white matter (82% of mass)

16B N
61B non-N

0.7B N
8B non-N

Basal nuclei, diencephalon, midbrain, pons (8% of mass)

69B N
16B non-N

Cerebellum (10% of mass)
Neuronal communication (chemical synaptic transmission)

- 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 $\mu$, $\delta$, and/or $\kappa$ receptors, which serve as receptors for endogenous opioids such as endorphins.
- Abused opioids (morphine, fentanyl, hydrocodone, oxycodone, etc.) act as agonists (activators) primarily at $\mu$ receptors.
Fentanyl
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

- sensory information carried by neurons (peripheral nerves) to spinal cord
- enter spinal cord via the dorsal horn
- $\text{A}\delta$ and $\text{C}$ fibers specifically carry pain sensations
- $\text{A}\beta$ and other fibers carry normal touch and pressure signals
- opioid receptors are located only on $\text{A}\delta$ and $\text{C}$ 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

Opiate Withdrawal Timeline

- Start: Take your last dose
- 72 Hours: Physical symptoms at peak (chills, fever, body aches, diarrhea, insomnia, muscle pain, nausea, dilated pupils)
- 1 Week: Physical symptoms start to lessen (tiredness, sweating, body aches, anxiety, irritability, nausea)
- 2 Week: Psychological and emotional symptoms (depression, anxiety, irritability, restlessness, trouble sleeping)
- 1 Month: Cravings and depression (symptoms can linger for weeks or months)

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

KRATOM
Opioids and polysubstance abuse

- Multiple drugs are often used with opioids.
- Alcohol and benzodiazepines (i.e., Xanax, Ativan, Valium) are often self-medicated symptoms of withdrawal.
- Stimulants such as cocaine and methamphetamine used to counteract opioid-induced sedation.
- All increase the risk adverse events and overdose.

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63% of all opioid deaths also involved other drugs.

Overdose Deaths Involving Benzodiazepines and Opioids, 2008-2018
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

- 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 *

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- 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

- 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?