Opioids, Overdose, and Fentanyls
Outline:

What are opioids?

Why are we experiencing and “opioid crisis”?

Potency, purity, and product

How do opioids cause overdose and overdose deaths?

What is naloxone and how does it work?
What is an opioid?:

Any chemical that activates opioid receptors can be called an opioid, including:

- chemicals produced in the human brain, e.g. endorphins
- chemicals found in nature, e.g. morphine, codeine
- modified versions of natural opioids, e.g. oxycodone, heroin
- fully synthetic chemicals, e.g. fentanyl, meperidine
What is an opioid receptor?:

A protein found in many cell types, including brain cells, that interacts with opioids and mediates their effects.

The three main types of opioid receptors are:

μ “Mu”
δ “Delta”
κ “Kappa”
Why fentanyls?:

Fentanyl is a potent opioid, used in anesthesia, for pain, chronic pain, pain in end of life care

Typically administered as a patch placed on the skin

Fentanyl is produced by pharmaceutical manufacturers

Small chemical changes to fentanyl can result in drugs with very similar actions

These “bootleg” or “illicit” fentanyls are not produced in regulated manufacturing facilities
(a) Fentanyl

(b) Acetyl fentanyl

(c) (Iso)butyryl fentanyl

(d) Ocfentanyl
Potency, purity, and product:

Potency describes how much of a drug you need to get an effect

Purity describes how much of the active opioid is present

Product is what the patient or the user will use
Why do we have an opioid crisis?: short answer :)

North America has relatively high opioid prescribing rates

We have manufactured products that are easy to use to achieve euphoria:

OxyContin
- could be crushed to get at high doses of oxycodone

Fentanyl patches
- 3 days worth of fentanyl could be extracted from a patch

High strength opioids
- contain a high dose of opioids per tablet or capsule
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What do opioids do?:

Activation of opioid receptors leads to:

- relief of pain and altered pain perception
- sedation and anesthesia
- cough suppression
- constipation/treatment of diarrhea
- miosis (small pupils)
- euphoria
- tolerance, dependence, addiction
- nausea and vomiting
- sweating
- respiratory depression
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Respiratory center

- Pneumotaxic Area
- Apneustic Area
- Inspiratory Area
- Expiratory Area

Medullary Rhythmicity Area

- Pons
- Medulla Oblongata
- Spinal Cord

https://lh5.googleusercontent.com/x18Lx7tc3BDy
Respiratory centre:

Normally, the respiratory centre controls breathing without any conscious control.

When oxygen levels fall (and carbon dioxide levels start to rise) the respiratory centre causes you to breath more and rapidly.

When oxygen levels are high (and carbon dioxide levels are low) breathing slows.
Opioid receptors in the respiratory centre:

Opioids interfere with respiratory centre function

Over-activation of opioid receptors make the respiratory centre less and less sensitive to rising carbon dioxide levels in the blood

Breathing becomes less frequent, more shallow, and ultimately stops during an opioid overdose
Respiratory centre depression and the “safety window”?

All CNS depressants could potentially cause respiratory depression and death.

A key question for a specific drug is - how much do you need to treat pain or achieve euphoria vs. cause respiratory depression.

For potent opioids, the difference between these 2 amounts gets smaller, and smaller, and smaller:
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Effective Dose (pure product)</th>
<th>Lethal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Carfentanil</td>
<td>0.001 mg</td>
<td>0.02 mg</td>
</tr>
</tbody>
</table>
Naloxone:

All opioids are opioid receptor AGONISTS (binds and activates the receptor)

Naloxone is opioid receptor ANTAGONIST (binds, but does **not** activate the receptor)

![Naloxone and Morphine Structures]

- **Naloxone**
- **Morphine**
Opioid overdose:

Lots of opioid over-activating the opioid receptors
Naloxone reverses the overdose:

By competing for opioid receptors and kicking off the opioid
Naloxone doesn’t last long:

Naloxone is metabolized faster than opioid agonists
Naloxone metabolism:

As naloxone levels fall, but the opioid remains, the overdoses could return