OPIATES AND OPIOIDS; CLINICAL AND CLINICAL PHARMACOLOGICAL ISSUES OF INTEREST

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STRUCTURE OF THE LECTURE

Ligand and receptor binding; receptors; receptors’ occupancy

Opiates’ receptors

The reward pathways

Potency of the different opiates/opioids

Desired effects

Related issues; tramadol; loperamide; kratom; gabapentinoids
The opioids includes four different groups of compounds:

"True opiates" natural alkaloids derived from the opium poppy (*Papaver somniferum*), such as morphine and codeine.

Semi-synthetic opioids, structurally related to morphine (heroin).

Synthetic opioids, structurally unrelated to morphine (fentanyl, methadone, pentazocine, etc).

Endogenous opioid peptides (*beta-endorphin, Met- and Leu-enkephalin, dynorphin A and B*); stereospecific opioid binding sites in the CNS.
THE OPIOID EPIDEMIC IN THE WESTERN WORLD

THE OPIOID EPIDEMIC

Opioid overdoses killed more than 33,000 people in the U.S. in 2015. Here we take a look at the drugs behind the opioid epidemic and available treatments for opioid overdose and addiction.

HEROIN & OPIOIDS

Like other opioids, heroin turns on opioid receptors to relieve pain and produce a feeling of euphoria. Opioids are highly addictive and at high doses can depress breathing, leading to death.

FENTANYL & ANALOGS

Fentanyl is a synthetic opioid that doctors prescribe to treat chronic pain. The fentanyl in street heroin is likely manufactured. Fentanyl analogs (selection shown below) are also increasingly common. Their higher potency increases the risk of overdose.

OVERDOSE & TREATMENT

Naloxone reverses the effects of opioid overdoses. It has a stronger affinity for opioid receptors than opioids do and turns off the receptors. The antidote works within two minutes when injected.

63.1% of drug overdose deaths in 2015 involved an opioid drug

Street heroin is now being mixed with other opioids, making it more potent and dangerous. Users often do not know what the heroin they are using contains, increasing the risk of overdose.

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A protein molecule, embedded in either the plasma membrane or cytoplasm of a cell, to which molecule may attach.

A molecule which binds to a receptor is called a "ligand," When such binding occurs, the receptor undergoes a conformational change which ordinarily initiates a cellular response.

Ligand-induced changes in receptors result in physiological changes which constitute the biological activity of the ligands.
Ligand binding is an equilibrium process. Ligands bind to receptors and dissociate from them according to the law of mass action.

One measure of how well a molecule fits a receptor is the binding affinity ($K_i$), which is inversely related to the dissociation constant $K_d$. A good fit corresponds with high affinity and low $K_d$.

The final biological response (e.g. second messenger cascade or muscle contraction), is only achieved after a significant number of receptors are activated.
LAW OF MASS ACTION

\[ L + R \leftrightarrow L \cdot R \quad K_d = \frac{[L][R]}{[L \cdot R]} \]
AGONISTS VERSUS ANTAGONISTS

The following classes of ligands exist:

*Full agonists* are able to activate the receptor and result in a maximal biological response. Most natural ligands are full agonists.

*Partial agonists* do not activate receptors thoroughly, causing responses which are partial compared to those of full agonists.

*Antagonists* bind to receptors but do not activate them. This results in receptor blockage, inhibiting the binding of other agonists.

*Inverse agonists* reduce the activity of receptors by inhibiting their constitutive activity.
Cells can increase (upregulate) or decrease (downregulate) the number of receptors to a given hormone or neurotransmitter to alter its sensitivity to this molecule. This is a locally acting feedback mechanism.

Prolonged or repeated exposure to a stimulus often results in decreased responsiveness of that receptor for a stimulus. Receptor desensitization results in altered affinity for the ligand
Effect of a drug: the response is related to the fraction of bound receptors. The fraction of bound receptors is known as occupancy.

The relationship between occupancy and pharmacological response is usually non-linear.
DOSE-RESPONSE CURVE

The graph shown represents the concentration-response for two hypothetical receptor agonists, plotted in a semi-log fashion. **The curve toward the left represents a higher potency** (potency arrow does not indicate direction of increase) since **lower concentrations are needed for a given response**. The effect increases as a function of concentration.
THE SYNAPSE TRANSMISSION

dopamine

dopamine receptor
DA NEUROTRANSMISSION
TRANSMEMBRANE G PROTEIN-COUPLED RECEPTORS; A FEW EXAMPLES

Muscarinic acetylcholine receptor

GABA receptors, Type-B

Cannabinoid receptors

Dopamine receptors

Opioid receptors
DOPAMINE AND THE PRODUCTION OF CYCLIC AMP
THE REWARD PATHWAY
LOCALIZATION OF OPIATE BINDING SITES
Schematic illustration of the way in which DA-containing neurons in the ventral tegmental area (VTA) are excited by opioids. **GABA-containing interneurons are hyperpolarized by opioids acting at mu-receptors.** This results in decreased (-) GABA release and **increased (+) firing** and DA release of DA-containing neurons in the VTA towards the nucleus accumbens (NAc).
OPIOIDS AND GABA-A RECEPTORS
OPIATES’ BINDING TO OPIATE RECEPTORS IN THE NUCLEUS ACCUMBENS: INCREASED DOPAMINE RELEASE
Three major subtypes of opiate receptor

- **μ (Mu, OP_3):** the most important receptor. Encoded by the MOR-1 gene, subtyped into μ_1 and μ_2. Agonists cause Supra–spinal & spinal analgesia, respiratory depression, euphoria, emetic effects, physical dependence, and constipation. Morphine and endorphines are selective agonist and naloxone is selective antagonist.

- **δ (Delta, OP_1):**Encoded by the DOR-1 gene. Subtyped into δ_1 and δ_2. Spinal analgesia, GI motility, motor integration, cognitive functions, mood driven behavior are the agonist properties. D-Ala-D-Leu-enkephalin is a selective agonists while naltrindole is a selective antagonist.

- **κ (Kappa, OP_2):** Learning & memory, spinal analgesia, sedation, neuroendocrine secretions. N/OFQ or ORL-1 receptor. Dynorphins are selective agonists.
# Selectivity for Different Receptors

## Opioids with their selectivity for different opioid receptors

<table>
<thead>
<tr>
<th>Opioid</th>
<th>MOP</th>
<th>KOP</th>
<th>DOP</th>
<th>NOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Morphine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>✓ Pethidine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>✓ Diamorphine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>✓ Fentanyl</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Partial agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Buprenorphine</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>✓ Pentazocine</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Naloxone</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

+ = low affinity; ++ = moderate affinity; +++ = high affinity; - = no affinity
MOP/DOP/KOP KNOCK-OUT MICE; THE RESULTING ISSUES

**MOR**
- **Mood**: Decreased anxiety- & depressive-like behaviors
- **Reward**: Abolished morphine, heroin & M6G CPP
  - Reduced ethanol, cocaine, nicotine & THC CPP
  - Reduced ethanol SA
  - Unchanged MDMA CPP
  - Reduced motivation to eat
  - Reduced maternal attachment

**KOR**
- **Mood**: Unchanged anxiety & depressive-like behaviors
  - Blunted stress-induced potentiation
  - Reinstatement of cocaine CPP
- **Reward**: Abolished kappa agonist CPA
  - Increased THC CPP
  - Unchanged morphine
  - Decreased nicotine SA

**DOR**
- **Mood**: Increased anxiety & depressive-like behaviors
- **Reward**: Increased oral ethanol SA
  - Followed by decreased anxiety
  - Unchanged THC CPP
  - Unchanged morphine SA
  - Decreased nicotine SA

TRENDS in Neurosciences
KOR ISSUES

CR845 Effects Mediated by Peripheral κ-Opioid Receptors

Novel Chemical Class – “hydrophilic” tetrapeptide

CR845 acts at KOR on:
- Immune cells: anti-inflammatory
- DRG: anti-nociceptive
- Sensory nerves: anti-nociceptive and anti-pruritic

BBB

DRG = dorsal root ganglion

KOR in the brain: dysphoria and hallucinations
### Opioid Peptides

<table>
<thead>
<tr>
<th>Genes for opioid peptides</th>
<th>Main opioid peptides</th>
<th>Preferred opioid receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepro-opiomelanocortin (POMC)</td>
<td>β-Endorphin, Met-enkephalin</td>
<td>µ (MOR, encoded by OPRM1) *Subtypes: µ₁, µ₂, µ₃</td>
</tr>
<tr>
<td>Prepro-enkephalin (PENK)</td>
<td>Met-enkephalin, Leu-enkephalin</td>
<td>δ (DOR, encoded by OPRD1) *Subtypes: δ₁, δ₂</td>
</tr>
<tr>
<td>Prepro-dynorphin (PDYN)</td>
<td>Dynorphin A, Dynorphin B, Neoendorphin</td>
<td>κ (KOR, encoded by OPRK1) *Subtypes: κ₁, κ₂, κ₃</td>
</tr>
<tr>
<td>Unknown</td>
<td>Endomorphin</td>
<td>µ (MOR, encoded by OPRM1)</td>
</tr>
</tbody>
</table>
# RECEPTORS AND LIGANDS

## Table 1. Opioid Receptor Type Classification

<table>
<thead>
<tr>
<th>Current NC-IUPHAR-Recommended Nomenclature(^1)</th>
<th>Previous Nomenclature</th>
<th>Presumed Endogenous Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$, $\mu$, or MOP</td>
<td>OP(_3)</td>
<td>$\beta$-endorphin (not selective) enkephalins (not selective) endomorphin-1(^2) endomorphin-2(^2)</td>
</tr>
<tr>
<td>$\delta$, delta, or DOP</td>
<td>OP(_1)</td>
<td>enkephalins (not selective) $\beta$-endorphin (not selective)</td>
</tr>
<tr>
<td>$\kappa$, kappa or KOP</td>
<td>OP(_2)</td>
<td>dynorphin A dynorphin B $\alpha$-neoendorphin</td>
</tr>
<tr>
<td>NOP</td>
<td>OP(_4)</td>
<td>nociceptin/orphanin FQ (N/OFQ)</td>
</tr>
</tbody>
</table>

**Footnotes:**

1. The well-established Greek terminology for opioid receptor types using the descriptors, $\mu$ (mu), $\delta$ (delta) or $\kappa$ (kappa), is recommended, but the receptor type should be additionally defined as MOP, DOP, KOP, or NOP when first mentioned in a publication.
2. No mechanism for the endogenous synthesis of endomorphins has been identified; their status as endogenous ligands for the $\mu$ opioid receptor is tentative.
OPIATES/OPIOIDS’ ANALGESIA

MECHANISM OF ACTION

- Opioid receptors are coupled with inhibitory G-proteins & their activation has a number of actions:

  - closing of voltage sensitive calcium channels,
  - stimulation of potassium efflux leading to hyperpolarization & reduced cyclic adenosine monophosphate (cAMP) production.

- Overall, the effect is a reduction in neuronal cell excitability - reduced transmission of nociceptive impulses.
How Buprenorphine Works

Opioid receptor is empty. As someone becomes tolerant to opioids, they become less sensitive and require more opioids to produce the same effect. Whenever there is an insufficient amount of opioid receptors activated, the patient feels discomfort. This happens in withdrawal.

Perfect fit – Maximum opioid effect. Opioid receptor filled with a full-agonist. The strong opioid effect of heroin and painkillers can cause euphoria and stop the withdrawal for a period of time (4-24 hours). The brain begins to crave opioids, sometimes to the point of an uncontrollable compulsion (addiction), and the cycle repeats and escalates.

Imperfect fit – Limited opioid effect. Opioids replaced and blocked by buprenorphine. Buprenorphine competes with the full agonist opioids for the receptor. Since buprenorphine has a higher affinity (stronger binding ability) it expels existing opioids and blocks others from attaching. As a partial agonist, the buprenorphine has a limited opioid effect, enough to stop withdrawal but not enough to cause intense euphoria.

Buprenorphine still blocks opioids as it dissipates. Over time (24-72 hours) buprenorphine dissipates, but still creates a limited opioid effect (enough to prevent withdrawal) and continues to block other opioids from attaching to the opioid receptors.

The above illustrations are for educational purposes and do not accurately represent the true appearance.
ESPRANOR; WHAT IS IT?

Dosage range: 2-18 mg

Bup-lyo relative to bup-SL:

1. Higher (25-30%) bioavailability, hence higher blood levels, with bup-lyo

2. Most CGL clients currently on bupren generic, hence one could wonder if there are even larger bioavailability differences in comparison with bup-lyo

3. Strang et al, 2017: ‘…we found substantially increased bioavailability of buprenorphine (but not of nor-buprenorphine) with "bup-lyo" relative to "bup-SL." In supervised dosing contexts, rapidly disintegrating formulations may enable wider buprenorphine prescribing.…’
ESPRANOR ISSUES

Removal of Espranor from the mouth is virtually impossible due to speed of disintegration (about 15 seconds)

Reduces the potential for concealment and removal of the dosage form once administered. This could reduce diversion, saving up of doses, or injection of crushed tablets

The oral lyophilisates have a mint flavouring (children attracted?) which may or may not be detectable by security dogs

Presence of gelatin; vegans/vegetarians’ possible concerns
## Potency in Comparison to Morphine

<table>
<thead>
<tr>
<th>Potency Relative to Morphine</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.0</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>2.0</td>
<td>Diamorphine (Heroin)</td>
</tr>
<tr>
<td>5.0</td>
<td>Hydromorphone (Dilaudid)</td>
</tr>
<tr>
<td>5.0</td>
<td>Levorphanol</td>
</tr>
<tr>
<td>1.0</td>
<td>Morphine</td>
</tr>
<tr>
<td>1.0</td>
<td>Oxycodone / Hydrocodone</td>
</tr>
<tr>
<td>1.0</td>
<td>Methadone</td>
</tr>
<tr>
<td>0.2</td>
<td>Propoxyphene (Darvocet)</td>
</tr>
<tr>
<td>0.125</td>
<td>Meperidine (Demoral)</td>
</tr>
<tr>
<td>0.01</td>
<td>Codeine</td>
</tr>
</tbody>
</table>
DIFFERENT OPIATES/OPIOIDS STRENGTHS

Opioid Strength Comparisons
CLINICAL EQUIVALENCE ISSUES

1 mg of Fentanyl is equal to:

66 mg Oxycodone
100 mg Morphine
1,000 mg Codeine
22,200 mg Ibuprofen
36,000 mg Aspirin
(taken orally)

Source: www.updates.pain-topics.org
By: Patrick McCarthy
OPIOIDS AND NSAIDS

**OPIOIDS**

- **Fentanyl**: 100:1
- **Buprenorphine**: 30:1
- **Methadone**: 10:1
- **Levorphanol**: 7:1
- **Oxymorphone**: 5:1
- **Hydromorphone**: 5:1
- **Oxycodone**: 1.3:1
- **Hydrocodone**: 1.2:1

**NSAIDS**

- **Morphine**: 1:1
- **Meloxicam**: 1:1.5
- **Diclofenac**: 1:5
- **Ketoprofen**: 1:5
- **Celecoxib**: 1:10

**Least Potent**

- **Propoxyphene**: 1:15

**Most Potent**

- **Aspirin (ASA)**: 1:130
- **Acetaminophen**: 1:130
- **Ibuprofen**: 1:40
- **Naproxen**: 1:50
# A Conversion Table

<table>
<thead>
<tr>
<th>Opioid</th>
<th>IV (mg)</th>
<th>PO (mg)</th>
<th>Interval/Duration (hr)</th>
<th>Onset (min)</th>
<th>Peak (min)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (MSIR)</td>
<td>10</td>
<td>30</td>
<td>3–4</td>
<td>IV 15–30</td>
<td>30–60</td>
<td>Injection: 2, 4, 8, 10, 15 mg/mL syringes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV &lt; 5</td>
<td>10–20</td>
<td>Oral soln: 10 mg/5 mL, 20 mg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PO 15–60</td>
<td>60</td>
<td>Suppositories: 5, 10, 20, 30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SC 5–10</td>
<td>20–60</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50–90</td>
<td></td>
</tr>
<tr>
<td>Morphine SR (MS Contin®, Kadian®, Avinza®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MS Contin (q12h): 15, 30, 60, 100, 200 mg tabs, Kadian (q12h): 20, 30, 60, 60, 80, 100 mg caps, Avinza (q24h): 30, 60, 90, 120 mg caps</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>1.5</td>
<td>7.5</td>
<td>8–12</td>
<td>IM 15–30</td>
<td>60</td>
<td>Tablets: 1, 2, 3, 4, 10 mg/mL; Oral Soln: 1 mg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV &lt; 5, PO 15–30</td>
<td>30–90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20–40</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30–90</td>
<td></td>
</tr>
<tr>
<td>Fentanyl inj. (Sublimaze)</td>
<td>0.1–0.2</td>
<td>0.2–0.4</td>
<td>3–4</td>
<td>IV 0.5–1</td>
<td>3–5</td>
<td>Injection: 50 mcg/mL</td>
</tr>
<tr>
<td>Fentanyl tab/loz. (Actiq, Fentora, Onsolis, Abstral)</td>
<td>0.2–0.4</td>
<td>0.2–0.4</td>
<td>1–2</td>
<td>PO: 1–2</td>
<td>10–30</td>
<td>Bioavailability different for each product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Buccal: 1–2</td>
<td></td>
<td>Dosing individual for each product</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Buccal 5–15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl patch (Duragesic)</td>
<td>72</td>
<td></td>
<td>8–12 hr</td>
<td>24–36 hr</td>
<td></td>
<td>25 mcg patch = 60 mg oral morphine/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patches: 12, 25, 50, 75, 100 mcg/hr</td>
</tr>
<tr>
<td>Methadone</td>
<td>See comments</td>
<td></td>
<td>6–12</td>
<td>IV 10–20</td>
<td>30–60</td>
<td>PO morphine:methadone ratio (mg/day):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PO 30–60</td>
<td></td>
<td>&lt; 90 mg (4:1); 90–300 mg (8:1); &gt; 300 (12:1)</td>
</tr>
<tr>
<td>Oxycodeone (Oxycotin (CR), OxylIR)</td>
<td>20</td>
<td></td>
<td>3–4</td>
<td>PO 10–15</td>
<td>30–60</td>
<td>morphine:oxycodeone ratio: 3:2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR 3–4</td>
<td></td>
<td>25% will require q8hr dosing with Oxycodeone CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td></td>
<td>3–4</td>
<td>PO 10–20</td>
<td>30–60</td>
<td>Lortab, Norco: 5, 7, 5, 10 mg (500, 325 mg)</td>
</tr>
</tbody>
</table>
# Different Opiates/Opioids’ Kinetics

<table>
<thead>
<tr>
<th>Kinetic Parameters (Chart)</th>
<th>oral bio-availability (avg)</th>
<th>onset of effect</th>
<th>average half life (hr.)</th>
<th>plasma protein binding</th>
<th>typical duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>codeine</td>
<td>70-90%</td>
<td>45-60m</td>
<td>prodrug</td>
<td>7-25%</td>
<td>4-6h</td>
</tr>
<tr>
<td>pethidine</td>
<td>40-60%</td>
<td>20-40m</td>
<td>3-5h</td>
<td>60-80%</td>
<td>2-4h</td>
</tr>
<tr>
<td>morphine</td>
<td>30-40%</td>
<td>30-45m</td>
<td>2-4h</td>
<td>35%</td>
<td>3-4h</td>
</tr>
<tr>
<td>oxycodone</td>
<td>60-80%</td>
<td>45-60m</td>
<td>3.5h</td>
<td>45%</td>
<td>4-6h</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>60-80%</td>
<td>45-60m</td>
<td>3.5h</td>
<td>unknown</td>
<td>4-6h</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>24%</td>
<td>30m</td>
<td>2.6h</td>
<td>8-19%</td>
<td>2-3h</td>
</tr>
<tr>
<td>oxymorphone</td>
<td>10%</td>
<td>20-40m</td>
<td>1.3h</td>
<td>10-12%</td>
<td>3-4h</td>
</tr>
<tr>
<td>levorphanol</td>
<td>-50%</td>
<td>20-40m</td>
<td>11-16h</td>
<td>40%</td>
<td>4-8h</td>
</tr>
<tr>
<td>methadone</td>
<td>80%</td>
<td>60-90m</td>
<td>22h</td>
<td>80-90%</td>
<td>6-12h</td>
</tr>
<tr>
<td>fentanyl</td>
<td>~10-15%</td>
<td>10-20m</td>
<td>3.5h</td>
<td>85%</td>
<td>1-2h</td>
</tr>
<tr>
<td>buprenorphine</td>
<td>~10-15%</td>
<td>60m</td>
<td>36h</td>
<td>96%</td>
<td>4-12h</td>
</tr>
<tr>
<td>tramadol</td>
<td>70%</td>
<td>60-90m</td>
<td>6-7h</td>
<td>20%</td>
<td>4-6h</td>
</tr>
<tr>
<td>tapentadol</td>
<td>30-40%</td>
<td>30-45m</td>
<td>4.5h</td>
<td>20%</td>
<td>2-4h</td>
</tr>
</tbody>
</table>
THE ANALGESIC LADDER

WHO Three-Step Analgesic Ladder

1. Non-opioid ± Adjuvant

2. Opioid for mild to moderate pain + Non-opioid ± Adjuvant

3. Opioid for moderate to severe pain ± Non-opioid ± Adjuvant

Freedom from cancer pain

Pain persisting or increasing
DECREASED LEVELS OF ANALGESIC EFFECTS OVER TIME?

Diminished opioid analgesic effects

Opioid tolerance
- Receptor desensitization
- Superactivation of cAMP pathway
**Therapeutic approaches:**
- Opioid dose escalation
- Use longer-acting opioids
- Add nonopioid analgesics
- Add drugs that prevent or delay tolerance

Opioid-induced hyperalgesia
- Sensitization of primary afferent neurons
- Activation of dynorphin and central glutamatergic systems
**Therapeutic approaches:**
- Tapering opioid doses
- Add NMDA antagonists
- Try longer-acting opioids
- Attempt rotation of opioids

Worsening pain state
- Disease progression
- Neuropathic pain mechanisms
- Enhanced opioid metabolism
**Therapeutic approaches:**
- Opioid dose escalation
- Add nonopioid analgesics
- Treat for neuropathic pain or other pain mechanisms
Clinical Effects of Opioids

Desirable effects
- Analgesia
- Relief of Anxiety

Undesirable effects
- Nausea/vomiting
- Urinary Retention
- Mental Status Changes
- Respiratory Depression
- Tolerance / Dry Mouth / Drug Dependence

Circumstantial effects
- Sedation
- Cough Suppression
- Euphoria
- Decreased Bowel Motility

OPIATES/OPIOIDS’ PSYCHOACTIVE EFFECTS

OPIOIDS or NARCOTICS

**Desirable Effects:**
- Euphoria
- Sedation
- Relief of anxiety and various other forms of distress
- Analgesia
- Depression of cough reflex*

**Subjective CNS effects:**
- Drowsiness
- Difficulty concentrating
- Apathy
- Decreased physical activity
- Lethargy
- Extremities feel heavy and the body feels warm
# Opiates/Opioids’ Intoxication and Withdrawal

## Table 2 – Signs and Symptoms of opioid intoxication and withdrawal

<table>
<thead>
<tr>
<th>Intoxication</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation or “rush” (with low dosages) and sedation/apathy (with high dosages)</td>
<td>Depressed mood and anxiety. Dysphoria</td>
</tr>
<tr>
<td>Euphoria or dysphoria</td>
<td>Cravin</td>
</tr>
<tr>
<td>Feelings of warmth, facial flushing, or itching</td>
<td>Piloerection, lacrimation or rhinorrhea</td>
</tr>
<tr>
<td>Impaired judgement, attention or memory</td>
<td>Frequently, “high” attention</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Hyperalgesia, joint and muscle pain</td>
</tr>
<tr>
<td>Constipation</td>
<td>Diarrhea and gastrointestinal cramping, nausea, or vomiting</td>
</tr>
<tr>
<td>Pupillary constriction</td>
<td>Pupillary dilatation and photophobia</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Respiratory depression, areflexia, hypotension, tachycardia</td>
<td>Autonomic hyperactivity (e. g., hyperreflexia, tachycardia, hypertension, tachypnea, sweating, hyperthermia)</td>
</tr>
<tr>
<td>Apnéia, sedação, coma</td>
<td>Yawning</td>
</tr>
</tbody>
</table>

*Source: Martin e Hubbard, 2000*
### Table 1: Clinical differentiation between opioid users for chronic pain and opioid abusers

<table>
<thead>
<tr>
<th></th>
<th>Opioid users for chronic pain</th>
<th>Opioid abusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of opioids</td>
<td>Appropriate</td>
<td>Out of control</td>
</tr>
<tr>
<td></td>
<td>Declared</td>
<td>Often deliberately omitted</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Improved by opioids</td>
<td>Impaired by opioids</td>
</tr>
<tr>
<td>Awareness of opioid-related side effects</td>
<td>Complete</td>
<td>Unconcerned</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Available</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Treatment plan and medical prescription</td>
<td>Followed</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Opioid medication</td>
<td>Available</td>
<td>Hidden, illicit</td>
</tr>
</tbody>
</table>
### Table 5. Medications for Rehabilitation from an Opioid-Use Disorder, According to the Patient’s Treatment Goal. *

<table>
<thead>
<tr>
<th>Stage or Function</th>
<th>Full Abstinence from Opioids</th>
<th>Opioid Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Naltrexone</td>
<td>Methadone</td>
</tr>
<tr>
<td>Action</td>
<td>Blocks opioid high</td>
<td>Long-term maintenance with the use of an oral, long-acting opioid</td>
</tr>
<tr>
<td>Restriction</td>
<td>Patient must be opioid-free</td>
<td>No misuse of depressant drugs or medical contraindications; can be used only in specialized programs, not in office-based practices</td>
</tr>
<tr>
<td>Induction and stabilization</td>
<td>Induction (on day 1): to ensure that drug does not cause withdrawal, administer 12.5–25 mg orally as a test; if no withdrawal, 4 hr later administer 25–50 mg orally; if no withdrawal on day 1, on day 2 initiate 50–100 mg orally daily</td>
<td>Induction and early stabilization (at wk 1 and 2): begin 15–30 mg orally and increase by 10–15 mg every 3–5 days up to 50–80 mg/day in most patients; late stabilization (at approximately wk 3–6): adjust dose according to side effects, craving, and adherence (usual dose, 80–100 mg/day)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>If patient is abstinent from opioids and cooperative, consider administration of 100 mg orally on Monday and Wednesday and 150 mg on Friday; may also consider switch to 380-mg depot injection once/mo</td>
<td>From approximately wk 6 to &gt;1 yr; at approximately 8 wk, consider weekend take-home doses if patient is adherent; consider weaning from methadone after &gt;1 yr‡</td>
</tr>
</tbody>
</table>

* Doses are approximate. All rehabilitation approaches should include cognitive behavioral therapy or similar counseling.

† This medication contains buprenorphine plus naltrexone in a ratio of 4 mg to 1 mg.

‡ Risks of returning to illicit-drug use and overdoses that may lead to death increase when maintenance is discontinued.
AND WHAT ABOUT THE POSSIBLE PHARMACOTHERAPIES OF THE FUTURE?

1. anti-craving medications

2. ultra-long-acting formulations, some of which have already been produced and are being studied or are in early clinical practice.

3. drug 'vaccines', whereby the body is stimulated to produce antibodies to, for example, cocaine and nicotine.
SLOW RELEASE ORAL MORPHINE (SROM)

Bond et al, 2012: ‘….slow-release oral morphine (SROM) is an acceptable maintenance medication in heroin users currently being prescribed injectable diamorphine/heroin, who are intolerant to supplementary methadone….’
RELATED ISSUES

tramadol
loperamide
kratom/MITragyna speciosa
gabapentinoids
TRAMADOL HYDROCHLORIDE

Discovered in Germany in 1970s; tramadol acts as a

1. μ-opioid receptor agonist
2. 5-HT releasing agent
3. NA reuptake inhibitor
4. NMDA receptor antagonist
5. 5-HT2C receptor antagonist

These serotonergic-modulating properties give it the potential to interact with other serotonergic agents increasing the risk of serotonin toxicity when tramadol is taken in combination with SSRIs

Tramadol is converted to O-desmethyl-tramadol, (‘Krypton’), two to four times more potent than tramadol itself
TRAMADOL DEPENDENCE AND TOLERANCE

Only limited international efforts to control abuse of tramadol at an international scale. In 2007, China took vigorous measures against tramadol marketing; this was associated with eventual decreasing levels of misuse in the general population.

Long-term use of high tramadol dosages may be associated with physical dependence and a withdrawal syndrome.

Withdrawal symptoms: composed of both typical opiate-like withdrawal symptoms and others, related to its effects on 5-HT/NA re-uptake. The atypical withdrawal symptoms may include those of SSRI discontinuation syndrome, such as: anxiety, depression, severe mood swings, aggressiveness, brain "zaps", electric shock-like sensations throughout the body, paresthesias, sweating, palpitations, restless legs syndrome, sneezing, insomnia, vivid dreams or nightmares, micropsia and/or macropsia, tremors, headache.
LOPE DOPE (SCHIFANO AND CHIAPPINI, 2018)

Loperamide is a common OTC anti-diarrhoeal compound, considered safe in the 2–16 mg daily dosage range.

Within these levels, due to a rapid metabolism and a poor blood–brain barrier penetration, loperamide may be lacking any abuse potential.

Loperamide is a potent mu-opioid receptor agonist with predominantly peripheral activity on the myenteric plexus, primarily decreasing intestinal propulsive activity.

Ingestion of higher, e.g. beyond 50 mg, loperamide dosages has however been associated with euphoria, central nervous system depression, and cardiotoxicity.
A growing trend in the number of published cases of loperamide toxicity from 2014 to 2016 has been identified.

Oral loperamide ingestion is characterized by less than 2% bioavailability levels.

Larger loperamide dosages or its combination with a molecule that will slow down the effectiveness of P-gp (e.g. quinine-quinidine) will produce a ‘great high’.

Since loperamide metabolism is related to CYP3A4 isozymes, its concomitant use with CYP3A4 (e.g. cimetidine, omeprazole, grapefruit juice, tonic water inhibitors) can increase loperamide plasma levels.

Loperamide supra-therapeutic dosages may be associated with cardiac arrest, recurrent syncope, ventricular tachycardia, and marked QT-interval prolongation.
**KRATOM (MITRAGYNA SPECIOSA)**

**Historical use**
Leaves CHEWED as an opiate substitute and stimulant in Thailand and South-East Asia (Thailandia, Malaysia, Borneo and New Guinea)

**Street names:**
Kratom, Ketum, Kakuam, Ithang, Thom, Mambog

**ROA:** chewed, smoked, brewed (tea, extract)
Several cases of **deaths reported**
Also found in *Krypton* herbal incense

**CONTRADICTORY EFFECTS**

↑↑↑↑↑doses ➔  opiate-like sedation ‘opiate-like dreamy reverie’

↓↓↓↓↓doses ➔  coca-like stimulation (alertness, energy, euphoria)
KRATOM LEAVES CONTAIN:

1) Mytragynine (or Biak-Biak)
   Partial agonist: μ-receptors, δ-opioid-receptors

2) 7-OH-mitragynine
   30-fold more potent μ-opioid agonist than 1)

3) Mitraphylline
   Agonism on μ- and δ-opioid-receptors as well as NMDA-antagonist

4) O-desmethyltramadol

Pregabalin and opiates/opioids: a frequent combination

- Gabapentinoids typically ingested by opioid addicts to potentiate the substitute opiates/opioids’ psychoactive effects; 15% of a sample in a drug addiction clinic in Germany were positive for both methadone and non prescribed pregabalin

- In animal studies, pregabalin has a potentiating effect when given to mice with existing opioid levels. This enhances pregabalin user’s vulnerability to develop abuse patterns and dependence, particularly among opioid dependent patients

- Gabapentin bioavailability may increase by 50% when co-administered with morphine
PREGABALIN and GABAPENTIN; binding affinity; potency; and pharmacokinetics’ considerations

- pregabalin binding affinity and potency is six times higher than that of gabapentin

- Pregabalin vs gabapentin higher addiction potential may be due as well to:
  - more rapid/non-saturable absorption (unaffected by agents that reduce gastrointestinal motility);
  - faster onset of action;
  - much faster attainment of maximum plasma concentration;
  - higher bioavailability (>90%, irrespective of the dosage).
Pregabalin pharmacodynamics

• Pregabalin: inhibitor of $\alpha 2\delta$-subunit-containing voltage-dependent calcium channels (VGCC; e.g. the $\alpha 2\delta$ type 1 and 2 proteins of the P/Q type of VGCCs).

• Entry of calcium ions into neurons allows the process of vesicle fusion with cell membrane/release of neurotransmitters.

• Hence, potent binding of pregabalin inhibit the trafficking of the $\alpha 2\delta$ subunit complex to the plasma membrane and reduce the synaptic vesicle exocytosis, with smaller levels of release of excitatory molecules: glutamate, noradrenaline and substance P but not dopamine

• gabapentinoids may act against aberrant neuronal excitation
Gabapentinoids and reward? Any direct/indirect dopaminergic activity?

- Microdialysis study: gabapentin (25–200 mg/kg, intraperitoneal, rats) produced a modest increase (approximately 50%) in extracellular nucleus accumbens GABA levels but failed to alter either the basal or the cocaine-enhanced dopamine activity in the reward system (Pengetal., 2008)

- Phenotypically, patients report pleasant stimulation and euphoria when using supra-therapeutic pregabalin doses (1,500-12,000 mg)

- in rats, conditioned place preference was induced only with higher (“supra-therapeutic”) intraperitoneal (but not oral) pregabalin doses
Pregabalin; liking and wanting

- Gabapentinoids could induce a “liking” (euphoric high) due to their GABA mimetic/de-sensitizing action but more limited levels of “wanting”/behavioural dependence (Berridge & Robinson 2016)

- Liking and wanting; what about the intake of supra-therapeutic dosages? Unclear

- There are several further nonregulated medications being deemed to have no relevant addictive potential (“wanting”) and observed to be abused preferentially by patients with a history of another substance use disorder: antidepressants (bupropion, tianeptine, venlafaxine); antipsychotics (quetiapine)
ANY QUESTIONS???

Thanks for your attention!!!