

Opioids											
<b>Receptors</b>	<p>1. <math>\mu</math> (MOP) <math>\rightarrow</math> most of the <b>analgesic</b> effects &amp; major <b>adverse effects</b></p> <p>2. <math>\delta</math> (DOP).</p> <p>3. <math>\kappa</math> (KOP) <math>\rightarrow</math> contribute to analgesia at the <b>spinal level</b></p>										
<b>MOA</b>	<p>1) <b>supraspinal analgesia</b>: activation of descending inhibitory pain control system</p> <p>2) <b>spinal analgesia</b>:</p> <ul style="list-style-type: none"> <li>- <b>presynaptic inhibition</b>: <math>\downarrow</math>Ca<sup>++</sup> influx <math>\rightarrow</math> <math>\downarrow</math> release of pain neurotransmitters (substance P &amp; glutamate)</li> <li>- <b>postsynaptic inhibition</b>: <math>\uparrow</math> K<sup>+</sup> efflux <math>\rightarrow</math> hyperpolarization</li> </ul>										
<b>Classification</b>	<table border="1"> <thead> <tr> <th>Strong <math>\mu</math> agonists</th> <th>Weak/moderate <math>\mu</math> agonists</th> <th>Partial <math>\mu</math> agonists / Mixed agonist-antagonists</th> </tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> <li>- <b>Morphine</b></li> <li>- <b>Meperidine</b></li> <li>- <b>Methadone</b></li> <li>- <b>Fentanyl</b></li> </ul> </td> <td> <ul style="list-style-type: none"> <li>- Codeine</li> <li>- Oxycodone</li> <li>- Hydrocodone</li> </ul> </td> <td> <ul style="list-style-type: none"> <li>- <b>Pentazocine</b> <math>\rightarrow</math> partial <math>\mu</math> agonist &amp; <math>\kappa</math> agonist</li> <li>- <b>Buprenorphine</b> <math>\rightarrow</math> partial <math>\mu</math> agonist &amp; <math>\kappa</math> antagonist</li> </ul> </td> </tr> </tbody> </table>	Strong $\mu$ agonists	Weak/moderate $\mu$ agonists	Partial $\mu$ agonists / Mixed agonist-antagonists	<ul style="list-style-type: none"> <li>- <b>Morphine</b></li> <li>- <b>Meperidine</b></li> <li>- <b>Methadone</b></li> <li>- <b>Fentanyl</b></li> </ul>	<ul style="list-style-type: none"> <li>- Codeine</li> <li>- Oxycodone</li> <li>- Hydrocodone</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Pentazocine</b> <math>\rightarrow</math> partial <math>\mu</math> agonist &amp; <math>\kappa</math> agonist</li> <li>- <b>Buprenorphine</b> <math>\rightarrow</math> partial <math>\mu</math> agonist &amp; <math>\kappa</math> antagonist</li> </ul>				
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<p><b>N.B. Pure opioid antagonists:</b></p> <ul style="list-style-type: none"> <li>- They have no analgesic effects.</li> <li>- Used to counteract S/E of <b>opioids overdose</b> and for the <b>treatment of opioid dependence</b>.</li> <li>- e. g: <b>naloxone</b> &amp; <b>naltrexone</b>.</li> </ul>											
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	<b>Prolongation of labor (except meperidine)</b>										
	<b>Urine retention</b>										
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<b>S/E</b> (Opioid Intoxications)	<p><b>Pharmacological effects +</b></p> <ul style="list-style-type: none"> <li>- <math>\uparrow</math>ICP (<b>CI in patients with closed-head injury</b>) <math>\rightarrow</math> Caused by CO<sub>2</sub>-induced VD of cerebral vessels</li> <li>- Exacerbation of pain in patients with biliary dysfunction or a gallbladder attack</li> <li>- Bronchospasm (<math>\uparrow</math>histamine)</li> </ul>										
	<p><b>TTT of acute opioid intoxication</b></p> <ul style="list-style-type: none"> <li>- Due to respiratory depression; Cases of overdose <b>need to be rapidly treated</b>.</li> <li>- <b>Naloxone</b> quickly displaces opioids bound to receptors and reverses respiratory depression.</li> </ul>										

Chronic opioid intoxication, opioid use disorder; OUD			
	Tolerance	Physical dependence	Psychological dependence
<b>Definition</b>	Decrease in the pharmacologic effect after repeated drug administration	Physiological state in which a person's continued use of an opioid is required for their well-being	condition in which individual feels compelled to repeatedly administer a psychoactive drug
<b>Features</b>	<ul style="list-style-type: none"> <li>- Cross-tolerance</li> <li>-Primarily from down-regulation of <math>\mu</math> receptors with repeated administration</li> <li>-Develops to most effects <b>but not to miosis &amp; constipation</b></li> <li>-Also <b>develops to respiratory depression</b>, still a sufficiently <b>high dose can still be fatal</b> to highly tolerant individuals</li> </ul>	<p><b>Opioid withdrawal syndrome</b></p> <ul style="list-style-type: none"> <li>-Equilibrium is disturbed and a rebound hyperexcitability occurs due to <b>abrupt withdrawal</b> or <b>use of antagonist</b></li> <li>- <b>A state of irritable &amp; aggressive behavior, plus:</b> <ol style="list-style-type: none"> <li>1-Fever and sweating &amp; Tachycardia.</li> <li>2-GIT upset &amp; abdominal cramps</li> <li>3-Piloerection.</li> <li>4 -<b>Pupillary dilation</b> (important sign) (opioid intoxication causes pinpoint pupils).</li> </ol> </li> </ul> <p><b>N.B.</b> Withdrawal isn't life-threatening</p>	<ul style="list-style-type: none"> <li>-<b>Physical dependence</b> occurs to avoid physical withdrawal symptoms</li> <li>-<b>Psychological dependence</b> occurs for a psychological reason</li> </ul>

**Treatment of opioid dependence (OUD)**

<b>Aim</b>	-Help <b>reduce symptoms of withdrawal</b> and maintain abstinence from other illicit use		
		Phase 1	Phase 2
	Description	Medically supervised opioid withdrawal ( <b>detoxification</b> )	Opioid replacement, <b>maintenance</b> , or substitution therapy
	Definition	Administration of a drug to reduce the severity of withdrawal Symptoms	Replacing an opioid with a longer acting but less euphoric and less addictive opioid
	Commonly used drugs	<b>1) Long-acting agonists:</b> buprenorphine & methadone <b>2) <math>\alpha</math>-2 adrenergic agonists:</b> clonidine	<b>1) Agonists:</b> buprenorphine & methadone. <b>2) Antagonists:</b> naltrexone <b>N.B.</b> Naltrexone can <b>trigger withdrawal</b> in opioid abusers, so <b>Phase 1 is needed before starting it</b>

**Adjunct drugs**

- 1)  **$\alpha$ -2 adrenergic agonists (clonidine)** → decrease anxiety associated with opioid withdrawal.
- 2) **Benzodiazepines or other sedating drugs** → to treat anxiety and insomnia associated with opioid withdrawal.
- 3) **Anti-diarrheal and antiemetic drugs**
- 4) **NSAIDs (naproxen)** → to relieve pain

<b>Morphine (Standard Opioid)</b>	<p><b>Kinetics:</b></p> <ul style="list-style-type: none"> <li>-Undergoes <b>significant first-pass metabolism</b></li> <li>-<b>6-glucuronide metabolite</b> → more active &amp; longer <math>t_{1/2}</math> than morphine → <b>enhances analgesic effect</b>.</li> </ul> <p><b>Uses:</b> Severe pain (associated with trauma, MI, cancer), <b>Acute pulmonary edema</b></p>
<b>Dimorphine (Heroin)</b>	<ul style="list-style-type: none"> <li>-Twice as potent as morphine.</li> <li>-<b>Most abused illicit opioid.</b></li> <li>-Highly addictive → rapid brain entry after injection → causes intense euphoria (<b>rush</b>).</li> </ul>
<b>Fentanyl &amp; its derivatives</b>	<ul style="list-style-type: none"> <li>-<b>Most potent</b> opioid agonists.</li> <li>-<b>Long-acting transdermal patch</b> (Duragesic) → provides continuous pain relief for severe chronic pain.</li> </ul>
<b>Pethidine (meperidine)</b>	<ul style="list-style-type: none"> <li>-Equianalgesic to morphine.</li> <li>-No constipation or ↑ biliary pressure → used in pancreatitis.</li> <li>-<b>Does not prolong labor</b> → used for labor analgesia.</li> <li>-<b>Atropine-like effect</b> → ↑ HR → used in inferior MI.</li> <li>-Short-term use only → <b>toxic metabolite</b> (normeperidine) <b>can cause seizures in renal failure</b>.</li> </ul>
<b>Methadone</b>	<ul style="list-style-type: none"> <li>-Longer duration of action &amp; milder withdrawal.</li> <li>-Oral use for opioid dependence treatment</li> </ul>
<b>Codeine</b>	<ul style="list-style-type: none"> <li>-1/12 potency of morphine → used for mild to moderate pain (often combined with aspirin or acetaminophen).</li> <li>-Antitussive effects.</li> <li>-<b>Most constipating opioid.</b></li> <li>-Less addictive.</li> <li>-<b>Metabolized by CYP2D6</b> → liable to genetic polymorphism → variable patient response.</li> </ul>
<b>Tramadol</b>	<p><b>MOA:</b> <math>\mu</math>-receptor agonist &amp; inhibits neuronal reuptake of 5HT &amp; NE.</p> <p><b>Use:</b> Neuropathic pain.</p> <p><b>S/E:</b> Seizures (mainly).</p>