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**Opioid analgesic agents**

* Also called narcotic analgesic, or God-own medication, these drugs cause analgesia with sedation.
* Opium derived from opium poppy, the first isolate substance from opium called morphine related to Morpheus (the Greek God of dreams).

**Endogenous opioid peptides**: (endorphins, leucine-enkephalin, dynorphins.)

* The endogenous opioid peptides are derived from precursor proteins: prepro-opiomelanocortin (POMC), preproenkephalin (proenkephalin A), and preprodynorphin (proenkephalin B). The endogenous peptides endomorphin-1 and endomorphin-2 also possess many of the properties of opioid peptides, notably analgesia and high-affinity binding to the receptor. Endomorphin-1 and -2 selectively activate central and peripheral -opioid receptors.
* Dynorphin A is also found in the dorsal horn of the spinal cord, where it may play a critical role in the sensitization of nociceptive neurotransmission. Increased levels of dynorphin can be found in the dorsal horn after tissue injury and inflammation. This elevated dynorphin level is proposed to increase pain and induce a state of long-lasting hyperalgesia. The pronociceptive action of dynorphin in the spinal cord appears to be independent of the opioid receptor system but dependent on the activation of the bradykinin receptor. Moreover, dynorphin A can bind and activate (NMDA) receptor complex.
* Recently, a novel receptor-ligand system similar to the opioid peptides has been found. The principle receptor for this system is orphanin opioid-receptor-like subtype 1 (ORL1). Its endogenous ligand has been termed nociceptin or orphanin FQ, This ligand-receptor system is currently known as the N/OFQ system.
* The N/OFQ system is widely expressed in the CNS and periphery, reflecting its equally diverse biology and pharmacology. As a result of experiments using highly selective NOP receptor ligands, the N/OFQ system has been implicated in both pro- and anti-nociceptive activity as well as in the modulation of drug reward, learning, mood, anxiety, and cough processes and of Parkinsonism.

**Opioid receptors are of three types:**

1. mu receptor (µ):- mu1, mu2
2. Delta receptor (δ). ( All G-protein coupled receptors.)
3. Kappa receptor (k).

 **µ receptor lead to**:-

1. Analgesia.
2. Euphoria.
3. Respiratory depression.
4. Physical dependence.
* **Delta receptor lead to**:-
1. Analgesia.
2. Dysphoria.
3. Mydriasis.
* ***K* receptor lead to**:-
1. Analgesia.
2. Dysphoria.
	* Site of opioid receptor:-
3. Spinal cord.

All↓ pain transmission and ↓ release of excitatory neurotransmitters.

1. Brain.
2. Peripheral tissue.
* Opioid agonists inhibit the release of excitatory transmitters from these primary afferents, and they directly inhibit the dorsal horn pain transmission neuron. These include descending (modulatory) pathways. That inhibit pain transmission neurons.
* The endogenous release of endorphin produced by immune cells within injured or inflamed tissue represents one source of physiologic peripheral -receptor activation.

Classification:-

* **Opioid agonist :(**Morphine.,Codeine.,Fentanyl.,Methadone.)
* **Partial agonist (**Buprenorphine.Dezocine.Nalbuphine**.)**
* **Antagonist :(**Naloxone, nalmefen.Naltrexone.)

**Opioid agonist**

* **Mechanism Classification**
1. Block ca+ voltage channel at pre-synaptic terminal neuron so ↓ excitatory neurotransmitter release.
2. Open k+ channel at post-synaptic neuron lead to hyperpolarization, ↓ post-synaptic action.

Effect of morphine (pharmacodynamics)

1. **CNS**:-
2. Analgesia.
3. Euphoria.
4. Sedation and disrupt normal sleep.
5. Respiratory depression by ↓ respiratory center sensitivity to co2.
6. Cough suppression.
7. Miosis, nausea, vomiting.
8. Truncal rigidity.
9. cvs: -
10. Vasodilatation, due to histamine release, vasomotor inhibition and co2 retention.
11. Cerebral vasodilatation.
12. ↑ Intracranial pressure.
13. ↓ Pulmonary vascular pressure.
14. respiratory system:-

Bronchoconstriction.

1. Due to histamine release
2. ↓ pulmonary ventilation.
3. GIT:-
4. Constipation
5. ↑ intra-biliary pressure, due to constriction of sp sphincter of oddi.
6. ↑ anal sphincter constriction.
7. Urinary tract:-
8. ↓ renal blood flow.
9. Urinary retention.
10. ↑ ADH, ↓ urine formation.
11. Uterus: ↓ uterine tone.(frequency and duration)
12. Endocrine
13. ↑ prolactin, ADH, ↑growth hormone.
14. ↓ other hormones
15. Other
16. Flushing, itching, sweating.
17. ↓ Lymphocyte proliferation.

**Indications of opioid agonist**

1. Analgesia for all types of pain, except:-
	* Head injury.
	* Renal colic
	* Biliary colic.
2. Acute pulmonary edema.
3. Cough.
4. Diarrhea.
5. Anesthesia.
6. Terminal illness.

**Contraindications**

1. Addison disease.
2. Asthma.
3. Hepatic disease.
4. Pregnancy.
5. Head injury.

**Side effects**

* Dependence and tolerance.
* Allergic reaction.
* Teratogenicity.
* Withdrawal-syndrome
* .
* Morphine metabolized by liver glucoronide to form morphine 6-glucoronide which is polar but more potent than morphine.
* Highly subjected to first – pass metabolism.
* **Pethidine (meperidine): it differs from morphine by**

|  |  |
| --- | --- |
| Morphine | Pethidine |
| Potent | Less potent |
| Natural | Synthetic |
| ↓H.R | ↑ H.R (-ve inotropic) | Antimuscarinic effects |
| Miosis | Mydriasis |
| Metabolized by glucoronide | Metabolized by demethylation |
| CNS depressant | CNS stimulant |
| Constipation | Less |
| Cough suppression | Less |
| More dependence | Less |
| Lipid soluble | Less |
| Not safe in labor | Safe |

* **Methadone:** Pure opioid agonist, similar to morphine but is long acting, not subjected to first – pass metabolism, not cause dependence, so used for morphine dependence.
* **Codeine**: Mild to moderate agonist, converted by liver to morphine, used as analgesic, it combine with acetominaphen and aspirin.
* **Propoxyphene**: Related to methadone but less analgesic, it combines with aspirin or acetominaphen.

**Diphenoxylate** and its metabolite, difenoxin, are not used for analgesia but for the treatment of diarrhea. . Its potential for abuse is considered very low because of its limited access to the brain. However, due to action on peripheral opioid receptors and lack of effect on CNS receptors, can be used for treatment of neuropathic pain

**Mixed agonist and antagonist (partial agonist):**

1. **Nalbuphine (µ antagonist + k agonist).**
2. **Buprenotphine (µ partial agonist).**
3. **Butesrphanol (k agonist + µ partial agonist).**
4. **Pentazocine (k agonist + µ antagonist).**
5. **Dezocine (µ partial agonist).**

All partial agonist are not used with morphine because it will remove the analgesic effect (mediated by µ receptors) and potentiate the respiratory depression (mediated by k receptors).

**Opioid antagonist**

|  |  |
| --- | --- |
| Naloxone | Naltrexon |
| Short acting | Long acting |
| Parentral | Orally and parentrally |
| For opioid poisoning | Also for alcoholism |

Opioid antagonists precipitate the withdrawal syndrome.

**Nalmefene**, is a derivative of naltrexone, nalmefene is used for opioid overdose has a longer half-life (8–10 hours).

## Selective antagonists:

* [**Cyprodime**](http://en.wikipedia.org/wiki/Cyprodime) is a selective [**mu** opioid receptor](http://en.wikipedia.org/wiki/Mu_opioid_receptor) antagonist
* [**Naltrindole**](http://en.wikipedia.org/wiki/Naltrindole) is a selective [**delta** opioid receptor](http://en.wikipedia.org/wiki/Delta_opioid_receptor) antagonist
* [**Norbinaltorphimine**](http://en.wikipedia.org/wiki/Norbinaltorphimine) is a selective [**kappa** opioid receptor](http://en.wikipedia.org/wiki/Kappa_opioid_receptor) antagonist

### Opioid Dependence

Naltrexone helps patients overcome opioid addiction by blocking the drugs’ euphoric effects, similar to [disulfiram](http://en.wikipedia.org/wiki/Disulfiram) in alcohol dependence. Unlike when used for alcohol dependence, naltrexone has little effect on opiate cravings. Naltrexone has in general been better studied for alcohol dependence than in treating opioid dependence. A recent review of studies suggests that more studies are needed to show naltrexone's effectiveness in treating opioid dependence (and to compare naltrexone to other options such as [methadone](http://en.wikipedia.org/wiki/Methadone) and [buprenorphine](http://en.wikipedia.org/wiki/Buprenorphine)).

**Indications of naltrexon**

1. [Rapid detoxification](http://en.wikipedia.org/wiki/Rapid_detoxification)
2. [depersonalization disorder](http://en.wikipedia.org/wiki/Depersonalization_disorder)
3. [multiple sclerosis](http://en.wikipedia.org/wiki/Multiple_sclerosis)
4. [fibromyalgia](http://en.wikipedia.org/wiki/Fibromyalgia)
5. Tobacco Dependence
6. [self-injurious behaviors](http://en.wikipedia.org/wiki/Self-injury)
7. [kleptomania](http://en.wikipedia.org/wiki/Kleptomania)
8. [Trichotillomania](http://en.wikipedia.org/wiki/Trichotillomania)
9. [pornography addiction](http://en.wikipedia.org/wiki/Pornography_addiction)

**Tolerance to opioid is attenuated by a number of substances, including:**

1. [calcium channel blockers](http://en.wikipedia.org/wiki/Calcium_channel_blocker)
2. [NMDA antagonists](http://en.wikipedia.org/wiki/NMDA_antagonist), such as [dextromethorphan](http://en.wikipedia.org/wiki/Dextromethorphan), [ketamine](http://en.wikipedia.org/wiki/Ketamine), and [memantine](http://en.wikipedia.org/wiki/Memantine).
3. [cholecystokinin antagonists](http://en.wikipedia.org/wiki/Cholecystokinin_antagonist), such as [proglumide](http://en.wikipedia.org/wiki/Proglumide)
4. [phosphodiesterase inhibitor](http://en.wikipedia.org/wiki/Phosphodiesterase_inhibitor) [ibudilast](http://en.wikipedia.org/wiki/Ibudilast)

**Tramdaol:** Weak µ agonist, inhibit re-uptake of serotonin and noradrenalin, used for chronic neuropathic pain and acute pain.

## Mechanism of action

 μ-opioid receptor agonist, serotonin reuptake inhibitor,  norepinephrine reuptake inhibitor,  NMDA receptor antagonist,  nicotinic acetylcholine receptor antagonist and M1  M3 muscarinic acetylcholine receptor antagonist. Relative to tramadol, its active metabolite O-desmethyltramadol has far higher affinity for the μ-opioid receptor. 5-HT2C blockade or GABAA receptors at high doses account for its lowering of the seizure threshold, In addition, tramadol's major active metabolite, O-desmethyltramadol, is a high-affinity ligand of the [δ-](https://en.wikipedia.org/wiki/%CE%94-opioid) and κ-opioid receptors, and activity at the former receptor could be involved in tramadol's ability to provoke seizures in some individuals, as δ-opioid receptor agonists are well known to induce seizures. Tramadol undergoes hepatic metabolism via the cytochrome P450 isozyme CYP2B6, CYP2D6 and CYP3A4, being *O*- and *N*-demethylated to five different metabolites. Of these, *O*-desmethyltramadol is the most significant since it has 200 times the μ-affinity of (+)-tramadol, and furthermore has an elimination half-life of nine hours, compared with six hours for tramadol itself. The most common adverse effects of tramadol include nausea, dizziness, dry mouth, indigestion, abdominal pain, vertigo,vomiting, constipation, drowsiness and headache. Compared to other opioids, respiratory depression and constipation are considered less of a problem with tramadol. There are suggestions that chronic opioid administration may induce a state of immune tolerance although tramadol, in contrast to typical opioids, may enhance immune function. Some have also stressed the negative effects of opioids on cognitive functioning and personality.

## Medical uses

Tramadol is used primarily to treat mild-severe pain, both acute and chronic . Tramadol is sometimes used in with local anaesthetics, NSAIDs, anticholinergics .

**Tapentadol** is a centrally acting opioid analgesic  with a dual action as an agonist of the μ-opioid receptor and as a norepinephrine reuptake inhibitor (NRI). Unlike tramadol, it has only weak effects on the reuptake of serotonin and is a significantly more potent opioid with no known active metabolites. Tapentadol is not a pro-drug and therefore does not rely on metabolism to produce its therapeutic effects; this makes it a useful moderate-potency analgesic option for patients who do not respond adequately to more commonly used opioids due to genetic disposition (poor metabolizers of CYP3A4 and CYP2D6), as well as providing a more consistent dosage-response range among the patient population. Tapentadol general potency is somewhere between that of tramadol and morphine with an analgesic efficacy comparable to that of oxycodone despite a lower incidence of side effects. It is generally regarded as a weak-moderate strength opioid. It raises intracranial pressure so should not be used in people with head injuries, brain tumors, or other conditions which increase intracranial pressure. It increases the risk of respiratory depression so should not be used in people with asthma. As with other mu-opioid agonists, tapentadol may cause spasms of the sphincter of Oddi, and is therefore discouraged for use in patients with biliary tract disease such as both acute and chronic pancreatitis.

**Chronic pain managed by**

1. Mexiletine: block voltage sensitive Na channel, also called pn3/sns channel.
2. Conotoxin: block N – type ca+ channel.
3. NMDA receptor antagonist: like gabapentine.
4. Epibatidin: nicotin analogue, activate the nicotinic receptors.
5. Enkephalinase inhibitor: like thiorphan, block encephalin degradation and produce morphine like analgesia without dependence.
6. Somatostatin, calcitonin: powerful analgesics when given intrathecally.
7. Substance P antagonist.
8. Adenosine kinase inhibitor: ↑ adenosine level which block pain pathway.
9. Ziconotide, a blocker of voltage-gated N-type calcium channels, is approved for intrathecal analgesia in patients with refractory chronic pain.

An **enkephalinase inhibitor** is a type of enzyme inhibitor which inhibits one or more members of the enkephalinase class of enzymes that break down the endogenousenkephalin opioid peptides like include racecadotril.

**Racecadotril**, also known as **acetorphan**, is an antidiarrheal drug which acts as a peripherally acting enkephalinase inhibitor. Unlike other opioid medications used to treat diarrhea, which reduce intestinal motility, racecadotril has an [antisecretory](https://en.wiktionary.org/wiki/antisecretory%22%20%5Co%20%22wikt%3Aantisecretory) effect—it reduces the secretion of water and electrolytes into the intestine.

 **Thiorphan** is the active metabolite of the antidiarrheal racecadotril (acetorphan). It prevents the degradation of endogenous enkephalins by acting as an enkephalinase inhibitor.

**Opiorphin**  from human saliva has a painkilling effect greater than that of morphine. It works by stopping the normal breakup of enkephalins, natural pain-killingopioids in the spinal cord.  Therapeutic application of opiorphin in humans would require modifying the molecule to avoid its rapid degradation in the intestine and its poor penetration of the blood–brain barrier.

**Spinorphin** is an endogenous, non-classical opioid peptide  isolated from the bovine spinal cord and acts as a regulator of the enkephalinases, , It does act by inhibiting the  aminopeptidase , dipeptidyl peptidase III (DPP3),angiotensin-converting enzyme (ACE), and neutral endopeptidase .  It has been observed to possess antinociceptive, antiallodynic, and anti-inflammatory properties. The mechanism of action of spinorphin has not been fully elucidated (i.e., how it acts to inhibit the enkephalinases), but it has been found to act as an antagonist of the P2X3 receptor, and as a weak partial agonist/antagonist of the FP1 receptor (**Formyl peptide receptor 1**)

### Opioid-induced hyperalgesia

Opioid-induced hyperalgesia has been observed in some patients, whereby individuals using opioids to relieve pain may paradoxically experience more pain as a result of their medication. causing hyperalgesia and allodynia, sometimes accompanied by a worsening of neuropathic pain, may be consequences of long-term treatment with opioid analgesics, especially when increasing tolerance has resulted in loss of efficacy and consequent progressive dose escalation over time. This appears to largely be a result of actions of opioid drugs at targets other than the three classic opioid receptors, including the nociceptin receptor, sigma receptor and Toll-like receptor 4,. No drugs are currently approved specifically for counteracting opioid-induced hyperalgesia in humans and in severe cases the only solution may be to discontinue use of opioid analgesics and replace them with non-opioid analgesic drugs. However, since individual sensitivity to the development of this side effect is highly dose dependent and may vary depending which opioid analgesic is used, many patients can avoid this side effect simply through dose reduction of the opioid drug (usually accompanied by addition of a supplemental non-opioid analgesic), rotating between different opioid drugs, or by switching to a milder opioid with mixed mode of action that also counteracts neuropathic pain, particularly tramadol or tapentadol.

**النفس تبكي على الدنيا وقد علمت أن السعادة فيها ترك ما فيها
لا دار للمرء بعد الموت يسكنها إلا التي كان قبل الموت بانيها
فإن بناها بخير طاب مسكنه وإن بناها بشر خاب بانيها
أموالنا لذوي الميراث نجمعها ودورنا لخراب الدهر نبنيه**

**لا تركنن إلى الدنيا وما فيها فالموت لا شك يفنينا ويفنيها
لكل نفس وان كانت على وجل من المنية أمال تقويه**