

Analgesic, Antipyretic and Anti-inflammatory Drugs

Analgesics:

An analgesic or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain.

Examples: Aspirin, Paracetamol.

Antipyretics:

Antipyretics are the drugs which reduce elevated body temperature up to the normal condition. They are also called antifebrile agents.

Certain analgesics and antipyretic agents may also possess anti-inflammatory properties.

Examples: Aspirin, Ibuprofen.

Anti-inflammatory Drugs:

Anti-inflammatory drugs are the agents that reduce inflammation.

Some drugs may possess analgesic, anti-pyretic and anti-inflammatory properties simultaneously though **one or two of the properties may be dominating in one drug and other may be dominating in another.**

There are various methods of classification of analgesics. One of the most important classifications is based upon the **capacity of analgesic to produce addiction or not.** On this basis, analgesics are classified into two groups, such as-

1. **Narcotic analgesics:** Narcotic analgesics are those analgesics that can reduce pain and at the same time causes addiction. e.g., Morphine.
2. **Non- narcotic analgesics:** Non- narcotic analgesics are those analgesics that can reduce pain without causing addiction. e.g., Aspirin.

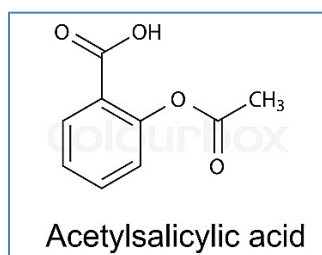
NSAIDs (Non-steroidal anti-inflammatory drugs)

Classification of NSAIDs:

NSAIDs can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action.

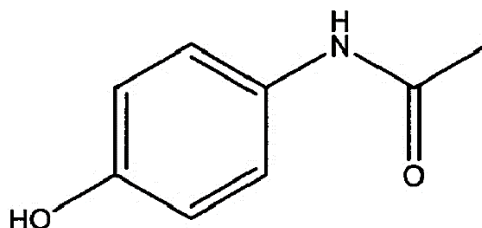
1. Salicylates / Salicylic acid derivatives:

- Aspirin (acetylsalicylic acid)
- Salicylic acid and other salicylates
- Salsalate (Disalcid)



2. Para-aminophenol derivatives:

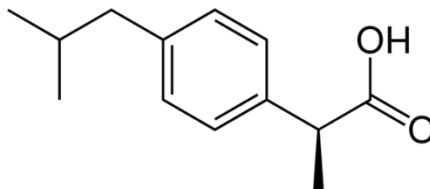
- Acetaminophen (Paracetamol)
- Phenacetin



Paracetamol

3. Propionic acid derivative:

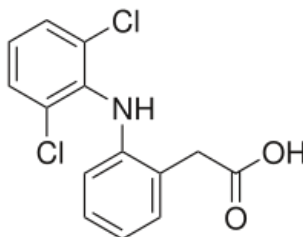
- Ibuprofen
- Dexibuprofen
- Naproxen
- Fenoprofen
- Ketoprofen
- Dexketoprofen



Ibuprofen

4. Acetic acid derivatives

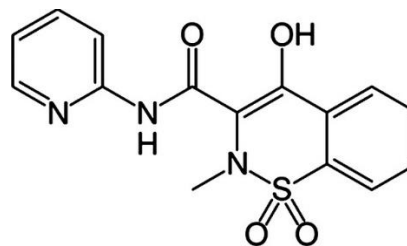
- Indomethacin
- Tolmetin
- Sulindac
- Etodolac
- Ketorolac
- Diclofenac
- Aceclofenac
- Nabumetone (drug itself is non-acidic but the active, principal metabolite has a carboxylic acid group)



Diclofenac

5. Enolic acid (Oxicam) derivatives

- Piroxicam
- Meloxicam
- Tenoxicam
- Droxicam
- Lornoxicam
- Isoxicam (withdrawn from market 1985)
- Phenylbutazone



Piroxicam

6. Anthranilic acid derivatives (Fenamates):

The following NSAIDs are derived from **fenamic acid**, which is a derivative of **anthranilic acid**, which in turn is a nitrogen isostere of salicylic acid, which is the active metabolite of aspirin.

- Mefenamic acid
- Meclofenamic acid
- Flufenamic acid
- Tolfenamic acid

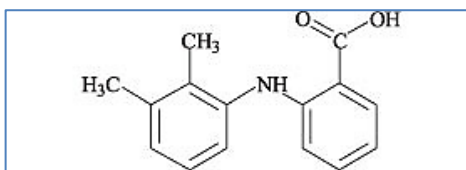
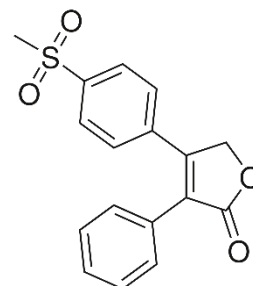


Figure 1. Chemical structure of mefenamic acid.

Selective COX-2 inhibitors (Coxibs):

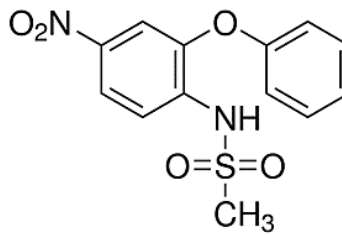
- Celecoxib (FDA alert)
- Rofecoxib (withdrawn from market)
- Valdecoxib (withdrawn from market)
- Parecoxib FDA withdrawn, licensed in the EU
- Etoricoxib not FDA approved, licensed in the EU



Rofecoxib

7. Sulfonanilides:

- Nimesulide (systemic preparations are banned by several countries for the potential risk of hepatotoxicity.)

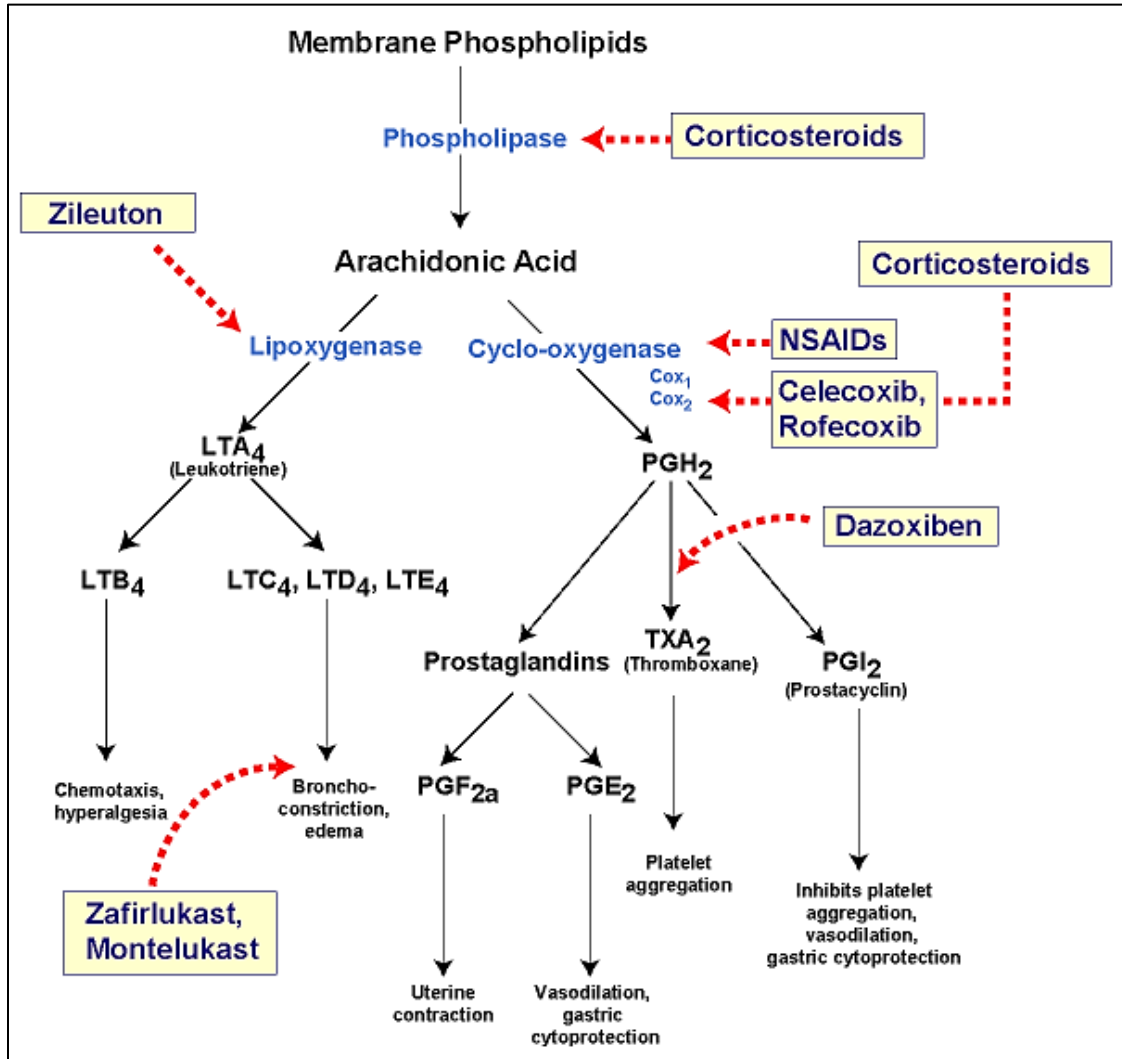


Nimesulide

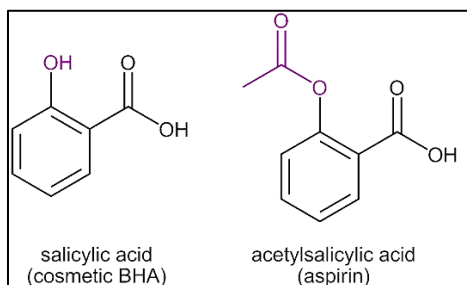
8. Others:

- Clonixin
- Licoferone acts by inhibiting LOX (lipoxygenase) & COX and hence known as 5-LOX/COX inhibitor.

Pharmacodynamics / Mechanism of action of NSAIDs:



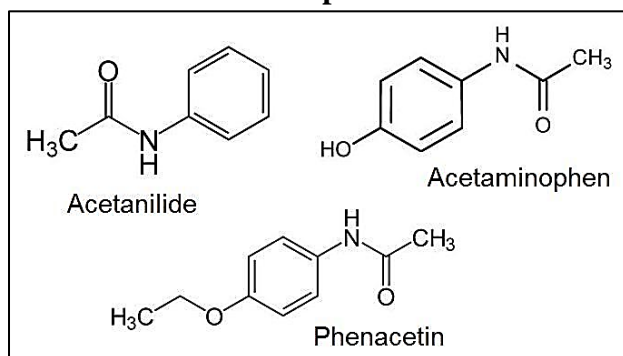
1. Salicylates / Salicylic acid derivatives



Major Actions:

- Analgesic (Analgesia)
 - Antipyretic
 - Anti-inflammatory
- **Analgesic effects:** They are used in **low intensity pain of limited or widespread origin**. e.g., headache, myalgia (pain in a muscle or group of muscles). Salicylates act by inhibiting synthesis of prostaglandins in inflamed tissues.
 - **Antipyretic action:** They reduce **elevated body temperature** up to the normal condition.
 - **Anti-inflammatory effects:** They help in reducing inflammation.
 - **Neurological effects:** High doses may cause convulsion, depression, confusion, tinnitus (perception of noise or ringing in the ears) deafness, dizziness, nausea, vomiting, coma etc.
 - **G.I effects:** They cause nausea, vomiting, gastric ulceration and hemorrhage, dyspepsia, gastric bleeding etc.
 - **On blood:** They cause **prolongation of bleeding time**.

2. Para-aminophenol derivatives



Acetanilide was introduced into therapy in **1886** as an antipyretic, analgesic but was found to be toxic due to **methemoglobinemia** (**Abnormal amount of methemoglobin is produced**. Methemoglobin is an oxygen-carrying metalloprotein hemoglobin, in which the iron in the heme group is in the Fe^{3+} state, not the Fe^{2+} of normal hemoglobin) **and jaundice**.

Phenacetin was introduced on **1887** and was widely used but withdrawn because of persistent reports of **nephrotoxicity**.

Acetaminophen (Paracetamol) was subsequently **introduced in 1893** but remained unpopular for over 50 years **until it was observed that it is a metabolite of both acetanilide and phenacetin**. It remains the only useful agent of this group and is widely used as non-prescription antipyretic, analgesic whereas the analgesic activity of acetaminophen is comparable to aspirin. Its major advantage over aspirin as an analgesic is that **individuals who are hypersensitive to salicylates generally respond well to acetaminophen**.

Overdoses

Overdoses may cause fatal hepatic necrosis, renal tubular necrosis methemoglobinemia hemolytic anemia, and thrombocytopenia.

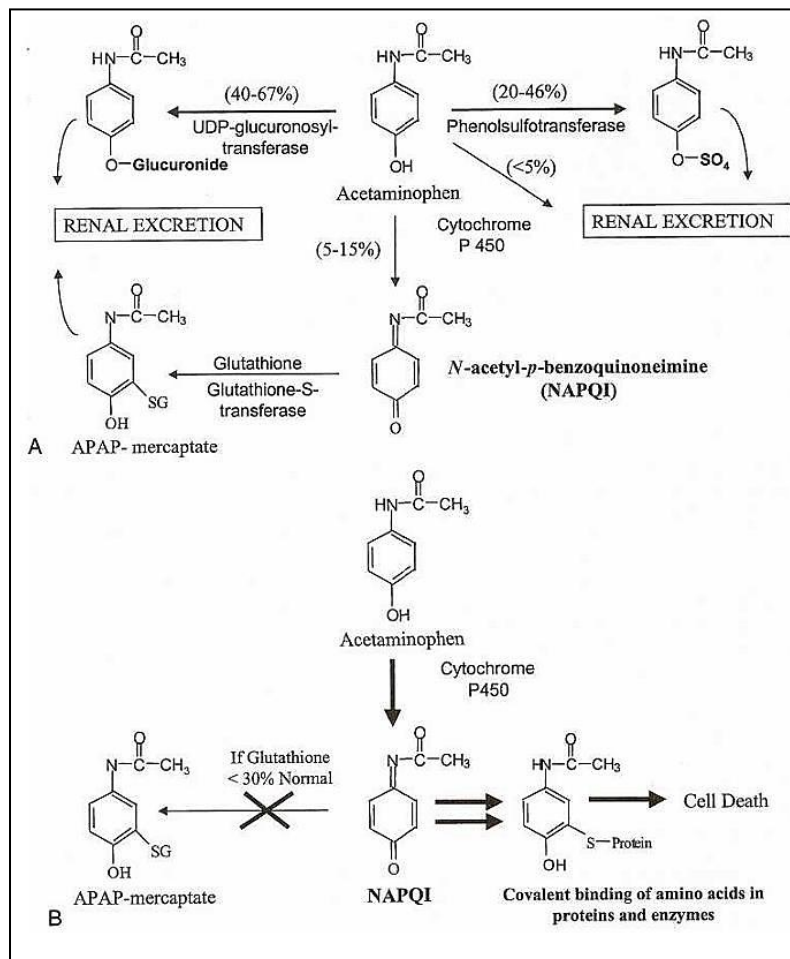
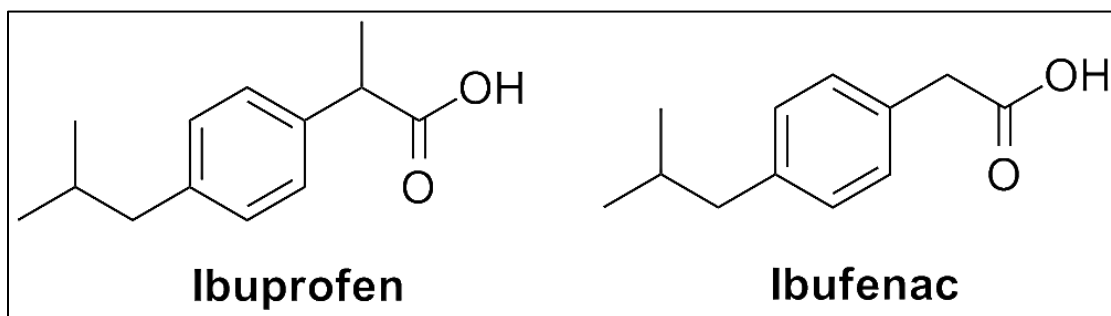


Figure: Metabolism of Paracetamol

3. Propionic acid derivative



During the Investigations on anti-inflammatory drugs, the **first successful outcome** was **Ibufenac**. But it was found to cause **liver damage in experimental animal**. It remained as a **successful successor**.

Simple modification of the Ibufenac molecule gave **Ibuprofen** available for **clinical use in 1969** with a **considerable success**.

Ibuprofen is used primarily for fever, pain, dysmenorrhea (painful menstruation, typically involving abdominal cramps) and inflammatory diseases such as osteoarthritis (**Osteoarthritis is caused by mechanical wear and tear on joints**) and rheumatoid arthritis (**Rheumatoid arthritis is an autoimmune disease in which the body's own immune system attacks the body's joints**). It is also used for pericarditis and patent ductus arteriosus (**ductus arteriosus fails to close after birth**).

Side effects are typically aspirin like e.g. GI upset with bleeding, disturbances of CNS function (headache, blurred vision, tinnitus), thrombocytopenia (deficiency of platelets in the blood).

4. Pyrazolone Derivatives

Phenylbutazone was originally made available for use in humans for the treatment of rheumatoid arthritis and gout in **1949**.

1. It gives anti-inflammatory effects by inhibiting the biosynthesis of prostaglandins, uncoupling of oxidative phosphorylation.
2. For pain of non-rheumatoid arthritis, analgesic efficacy is inferior to that of salicylates.
3. It is mild uricosuric (**Uricosuric medications**) drugs are substances that increase the excretion of uric acid in the urine, thus reducing the concentration of uric acid in blood plasma. In general, this effect is achieved by action on the proximal tubule of the kidney) in man which results from diminished tubular reabsorption of uric acid.

Side effects

The most common side effects of phenylbutazone involve the gastrointestinal system. It can also cause ulcerations, abdominal burning, pain, cramping, nausea, gastritis, and even serious gastrointestinal bleeding and liver toxicity, nephritis, aplastic anemia (deficiency of all types of blood cell caused by failure of bone marrow development), leucopenia (reduction in the number

of white cells in the blood, typical of various diseases), thrombocytopenia (deficiency of platelets in the blood. This causes bleeding into the tissues and slow blood clotting after injury), nervousness, blurred vision.

Therefore, **it is often desirable to use the lowest effective dose to minimize side effects.**

5. Indole and indene acetic acid derivatives

It is used in patients with **acute post-operative and rheumatic pain of mild to moderate intensity.**

It is also used as antipyretic in Hodgkin disease (**Hodgkin lymphoma**) is a type of lymphoma, a cancer that starts in white blood cells called lymphocytes. Lymphocytes are part of the immune system. Cancer starts when cells in the body begin to grow out of control.

Indomethacin is also used to treat ankylosing spondylitis, which is a type of arthritis that affects the joints in the spine.

- It works by inhibiting the production of prostaglandins.
- It inhibits motility of polymorphonuclear leukocytes.

6. N-arylanthranilic acid derivatives

Meclofenamic acid is a drug used for joint, muscular pain, rheumatoid arthritis including menstrual pain. It is a member of the NSAID class of drugs and was approved by the FDA in 1980.

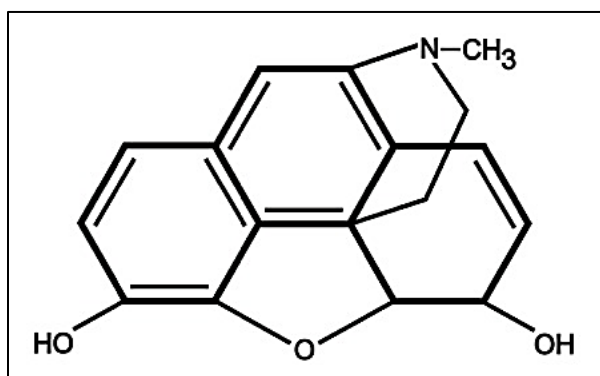
It inhibits the synthesis of prostaglandins.

Diclofenac is used to treat pain, inflammatory disorders, and dysmenorrhea. Inflammatory disorders may include arthritis, rheumatoid arthritis, osteoarthritis, dental pain, ankylosing spondylitis and gout .

Diclofenac is used as eye drops to treat acute and chronic nonbacterial inflammations of the anterior part of the eyes (e.g., postoperative states).

Narcotic analgesics

Narcotic analgesics are those analgesics that can reduce pain and at the same time causes addiction. e.g., Morphine.



The narcotic analgesics are also called opioid analgesics or opiates. They are mainly obtained from unripe capsules of *Papaver somniferum*. The important alkaloid isolated from opium is morphine. The other alkaloids isolated from opium are codeine, papaverine, and thebaine.

Opiate

Any natural or synthetic agent that was derived from morphine, i.e. structurally related to morphine.

Opioid

Opium like or morphine like in terms of pharmacological action. The broad group of opium alkaloids, synthetic derivatives related to the opium alkaloids and many naturally occurring synthetic peptides with morphine like pharmacological effects is called opioids. In addition to having pharmacological effects similar to those of morphine, a compound must be antagonized by an opioid antagonist such as naloxone to be classified as opioid.

Classification of opioid analgesic:

Opioid analgesics can be classified into seven groups:

1. Morphine analogues:

Morphine sulphate, Codeine phosphate, ethyl morphine, Diacetyl morphine (Heroin), Hydrocodone, Oxycodone, Dihydromorphine, Dihydrocodeine.

2. Morphinan analogues:

Levorphenol tartrate, Dextromethorphan, Butarphenol.

3. Morphan analogues:

Metazocin, Cyclazocine, Phenazocine, Pentazocine.

4. 4-Phenylpiperidine analogues:

Pethidine hydrochloride, Diphenoxylate hydrochloride, Fentanyl citrate.

5. Phenoxypropylamine analogues:

Methadone hydrochloride, Dextropropoxyphene hydrochloride.

6. Miscellaneous:

Tramadol, Nexeridine, Sulfentanil, Tilidate.

7. Narcotic antagonists:

Nalorphine, Naloxone, Naltrexene, Profadol, Propiram, Lavellorphan.

Mechanism of action of opioid analgesics / narcotic analgesics:

An opioid is an analgesic that **works by binding to opioid receptors** which are found principally in the **CNS and GIT**. The receptors in these two organ systems mediate both beneficial effects and the undesirable side effects. Opioid analgesics also known as narcotic analgesics are the pain relievers that act on the CNS. Like all narcotics, they may become habit forming if used over a long period.

The opium group of narcotic drugs is the most powerfully acting and clinically useful drugs producing depression of CNS. They depress the CNS and relieve pain. The term opioid is used generally to designate collectively the drugs (natural or synthetic) which bind specifically to any of sub-species of receptors of morphine and produce morphine like action.

They have five major side effects

- They have addictive properties
- They cause constipation.
- They cause decrease in GI motility
- They cause respiratory depression
- They increase biliary tract pressure

Therapeutic application of narcotic analgesic

- Relief of pain after surgery
- Diabetic neuropathy
- Labor pain.

Receptor:

Classification of opioid / opiate receptors:

Effects of Different Opioid Receptor Stimulation:			
	μ receptor	κ receptor	δ receptor
Location	$\mu 1$ - supraspinal $\mu 2$ - spinal	$\kappa 1$ - spinal $\kappa 3$ -supraspinal	Spinal supraspinal
Effects	Analgesia Respiratory depression Sedation Euphoria Miosis Physical dependence Loss of GI motility	Spinal analgesia Dysphoria Sedation Psychomimetic Physical dependence (nalorphine type) Pentazocine	Spinal analgesia Affective behaviour (Supraspinal) Respiratory depression Reduced GI motility
Agonists	Morphine, codeine, Fentanyl and pentazocine weakly		

Others,

Sigma – Dysphoria (Dysphoria is a profound state of unease or dissatisfaction), hallucination, respiratory depression and vasomotor stimulation.

Delta – Supraspinal analgesia, respiratory depression, euphoria and psychological dependence.

Analgesic effect: mediated by μ , κ receptors

Location of opioid receptors:

- CNS
- Nerve terminals in periphery
- Cells of gastrointestinal tract

Morphine

Mechanism of action:

- Morphine activates opiate receptor to produce analgesic effect like endogenous opiate peptides.
- High affinity for μ receptors
- Varying affinities for δ and κ receptors
- Low affinity for σ receptors in CNS and gastrointestinal tract.

Pharmacologic effects

1. Effects on CNS

- Analgesia and sedation: prominent effect.
- Emesis by direct stimulation of CTZ to cause nausea and vomiting.
- Respiratory depression by reducing response of respiratory centers to blood CO_2 .
- Suppression of cough by direct inhibition of cough center.
- Myosis (constriction of the pupil).

2. Cardiovascular effects

- Peripheral vasodilation to cause orthostatic hypotension
- Cerebral vasodilation to increase intracranial pressure

3. Gastrointestinal effects

- Relieves diarrhea or causes constipation
- Increasing biliary pressure

4. Other effects

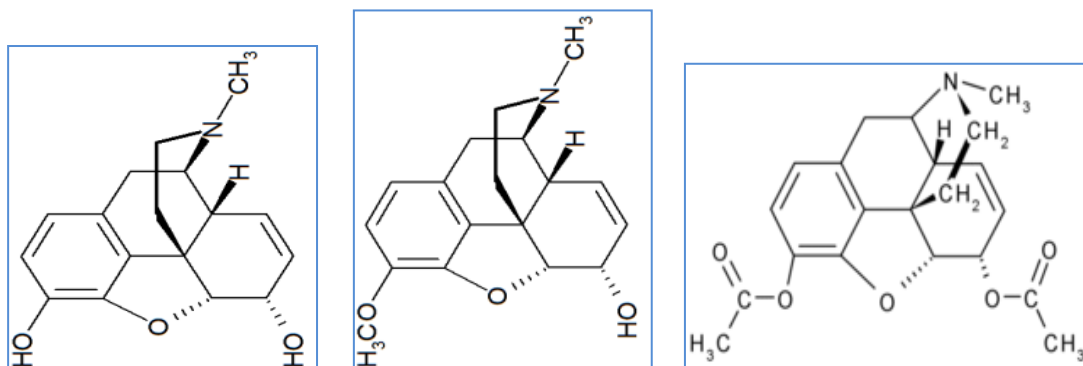
- Bronchoconstriction by histamine.

Heroin

- It is stronger analgesic than morphine
- It is powerful depressant
- It produces more intense euphoria.

Use: As with other opioids, it is used as a pain killer and recreational drug.

Q. Morphine is more potent than Codeine but less potent than Heroin. Why??



Heroin is synthesized from morphine by a relatively **simple esterification reaction**. The extra acetyl group makes the molecule **more hydrophobic and lipophilic** compared to morphine.

A possible reason may be that heroin passes the BBB (blood brain barrier) much more rapidly than morphine. Once in the brain, the heroin is hydrolyzed into morphine which is responsible for its activity.

One of the most common methods of heroin use is via intravenous administration. **If taken orally**, heroin undergoes extensive **first-pass metabolism via deacetylation** making it prodrug for the systemic activity for morphine.

When the drug is injected, it avoids first-pass effect and very rapidly crosses blood brain barrier due to the presence of the acetyl group which renders it much more lipid-soluble than morphine itself. **Once in the brain**, it is **deacylated into 3- and 6-monoacetyl morphine** which **bind to μ receptors** resulting in **intense euphoria, decreased pain perception and anxiolytic activity**.

Codeine is the **methyl ether of morphine**. Roughly only **5 to 10% of codeine is metabolized into morphine** with the remainder either free or conjugated to form codeine-6-glucuronide. For this reason, Morphine is more potent than Codeine but less potent than Heroin.

Morphine abstinence syndrome (Withdrawal syndrome)

All morphine like analgesic produces identical abstinence syndrome. Restlessness appears first with coldness resulting in increased nasal secretions and irregular respiration.

As the syndrome develops, there are painful abdominal cramps, vomiting, diarrhea, profuse sweating, muscle pain and violent muscle twitching. The patient may threaten violence.

There may be cardiovascular collapse which is fatal for older patient.

Methadone

- Methadone is often used to treat heroin addiction because it is a longer lasting opioid.
- It is also a morphine like analgesic and is also effective in the replacement of morphine like drugs of dependence. 1mg of methadone can replace 20mg of pethidine, 4mg morphine and 2 mg of heroin.
- It is used as cough suppressant.
- It has a half-life of 24 to 48 hours compared to 2 to 4 hours found with morphine and codeine.
- It is an analog of codeine and it was first synthesized in 1937.

Opioid Antagonists

- Opioid Antagonists are used to treat opioid overdose cases.
- Most are derived from thebaine (an alkaloid of Opium)
- They have strong binding affinity for the μ receptors
- They work by competitive inhibition at the binding site (It binds but does not change the receptor while at the same time blocking the agonist).

Nalorphine (Opioid antagonist):

- It has morphine like analgesic, respiratory and cough suppressant properties.
- It produces constriction of the pupil.
- In the presence of morphine, it antagonizes the effects.
- Its advantage is that it does not produce any physical and psychological dependence.