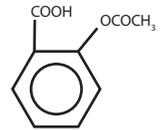


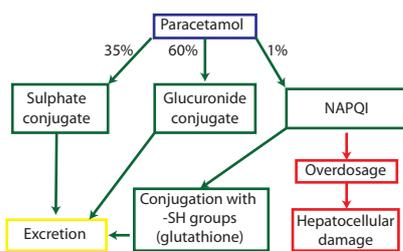
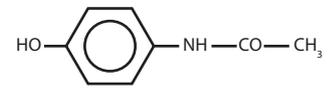
# NON OPIOID ANALGESICS and ANTI-INFLAMMATORY MEDICATIONS

**NSAIDs classification** can be based on their **cyclooxygenase selectivity**, on whether their enzyme inhibition is **irreversible or reversible** (aspirin versus others) or based on their **chemical structure**. With regards to the last method the following categories are noted; salicylates (aspirin), arylpropionic acid (ibuprofen, naproxen), arylacetic acids (diclofenac, ketorolac) and oxicams (meloxicam, piroxicam). The route of administration for NSAIDs is **usually oral**, there is **rapid absorption** through the **small bowel** (some are administered IV such as ketorolac, tenoxicam and parecoxib). NSAIDs are **highly protein bound** and have **low volumes of distribution**. The effects of highly protein bound drugs (such as **warfarin**) may become **potentiated** as they become displaced. Characteristically these drugs are **metabolised in the liver** and excreted in an **inactive form** in the urine and bile. Cyclooxygenase exists as **two isoenzymes COX-1 and COX-2**. COX-1 (the constitutive form) is responsible for the production of prostaglandins that control renal blood flow and form the protective gastric mucosal barrier. In addition COX-1 mediates the synthesis of thromboxane. A variant of COX-1 which has been called **COX-3 exists centrally** and is possibly the mechanism by which paracetamol reduces pain and pyrexia. **COX-2** (the inducible form) is produced in response to tissue damage and **facilitates the inflammatory response**. COX-2 also mediates the production of prostacyclin (PGI<sub>2</sub>) in vascular endothelium. As a result **COX-2 inhibitors may alter delicate thromboxane/prostacyclin balance** in favour of platelet aggregation, vasoconstriction and thromboembolism.

**Aspirin** is the **acetylated derivative of salicylic acid**, which is produced from the glycoside salicin obtained from willow bark. Aspirin is most commonly used for its **analgesic, antipyretic and anti-inflammatory effects**. It is most effective in low intensity somatic pain, rather than severe visceral pain. Aspirin also rapidly **reduces body temperature** in febrile patients. Bacterial pyrogens cause the release of the inflammatory cytokines IL-1 and TNF-alpha increasing central PGE2 production by COX-3. Aspirin inhibits COX-3 as well as COX-1 and COX-2, decreases prostaglandin synthesis in the hypothalamus, and thus reduces body temperature. The anti-inflammatory effects of aspirin are due to the **decreased synthesis of prostaglandins**, particularly by COX-2, although relatively high doses are usually required. Aspirin **irreversibly acetylates COX-1 in platelets**, decreasing thromboxane synthesis and reducing their adhesiveness and aggregation, so that the **bleeding time is prolonged**. A new generation of platelets must be formed from megakaryocytes before normal thromboxane production is restored. In adults, acute **overdosage** with aspirin leads to an **increase in metabolism** and a **rise in O2 consumption and CO2 production**, due to an **uncoupling of oxidative phosphorylation**. In addition, there are complex effects on acid-base balance. Toxic doses of aspirin produce a CSF acidosis, causing stimulation of the respiratory centre and increased ventilation, with a rise in pH and a fall in PaCO<sub>2</sub>. **Terminally, an acidotic state** due to respiratory and metabolic changes may occur. This is a common presentation of severe aspirin overdosage.



**Paracetamol** has **analgesic and antipyretic effects** that are similar to aspirin, but little or **no anti-inflammatory activity**. It is generally accepted that it has little effect on extracerebral COX-1 or COX-2, although it **inhibits central COX-3**. Consequently, it **prevents** the enhanced synthesis of **prostaglandin E2** in the **hypothalamus** during pyrexia, and thus **reduces** elevated body temperature. It has similar effects to aspirin on non-specific pain. Paracetamol is also **synergistic with opioid medications**, reducing the overall opioid requirement by 20-30%.



At normal therapeutic dosages, primarily hepatic metabolism to sulfate and glucuronide conjugates, while a small amount is metabolized by CYP2E1 to a **highly reactive intermediate**, N-acetyl-p-benzoquinoneimine (**NAPQI**), which is conjugated rapidly with glutathione and inactivated to nontoxic cysteine and mercapturic acid conjugates. At toxic doses (as little as 4 g daily) **glutathione conjugation becomes insufficient** to meet the metabolic demand causing an **increase in NAPQI** concentrations, which may cause **hepatic cell necrosis**.

The aim of treatment is to **replenish glutathione** and enact **supportive management**. The use of activated charcoal may be indicated in some patients. It is useful to **plot the serum paracetamol levels** against a **nomogram** to help predict likelihood of hepatocellular damage and help guide therapy. The standard therapy is **N-acetylcysteine infusions** which most toxicologists agree replaces glutathione, therefore reducing hepatocellular damage. **ALT** is generally to **most sensitive marker** of liver damage. **Renal damage** may also be prominent.

**NMDA Antagonists** The **activation** by excitatory amino acids (**glutamate**) of **spinal cord dorsal horn** N-methyl-D-aspartate (NMDA) receptors is essential for **development of central sensitisation** after tissue damage. The anaesthetic **ketamine** is a potent **NMDA receptor antagonist**, and relatively low dose ketamine given by subcutaneous or continuous infusion produces significant pain relief. A notable advantage of ketamine is that it is effective for both nociceptive and neuropathic pain, which presents as a burning stinging pain with allodynia and dysesthesias. It may be of **particular benefit** with pain of a **mixed nociceptive/neuropathic** nature such as cancer patients and burn victims. As discussed previously the **side effects** of this drug such as hallucinations limit its use.

**α<sub>2</sub> Adrenoceptor Agonists** **clonidine** and **dexmedetomidine** have been shown to provide effective analgesia after a variety of surgical procedures. Their use has concentrated on the spinal or epidural administration of clonidine to take advantage of the known **attenuating effect** of stimulating **spinal α<sub>2</sub> receptors on pain perception**. In particular agents such as clonidine **may reduce wind-up via inhibitory actions** at wide dynamic range neurones. In general α<sub>2</sub> agonists are **useful only as adjuncts** to conventional **opioid analgesics** because of **side effects** of sedation, hypotension, and bradycardia, which can be **marked**. Clonidine is also useful in opioid withdrawal states and the treatment of complex regional pain syndromes.

**Anticonvulsants** are useful for the alleviation of **neuropathic pain**. Drugs used include **carbamazepine, phenytoin, sodium valproate**, and the newer agents such as **gabapentin**. Suggested mechanisms of action include **frequency dependent block of sodium channels, calcium channel blockade**, and **potentiation of GABA inhibition** of spinal nociceptive pathways through either increased release or reduced breakdown. The **frequent adverse events** have limited their use. One meta-analysis has shown that in patients with **trigeminal neuralgia** the **NNT with carbamazepine** is only 2.6, but the **number needed to harm is a 3.4!** Common side effects include sedation, rashes, nausea, anorexia, dizziness, confusion, and ataxia. More serious side effects include blood dyscrasias, sub acute hepatic impairment, renal failure and Stevens-Johnson syndrome. The newer agents such a gabapentin have an improved safety profile but still precipitate the serious adverse events.

**Tricyclic antidepressants** are used to relieve **neuropathic pain**. All **potentiate noradrenergic activity** by inhibiting noradrenaline reuptake at nerve endings, probably in **descending modulatory inhibitory pain pathways**. The anti-depressants have **similar NNT and NNH profiles** to the anticonvulsants and are again effective for the treatment of neuropathic pain but are beset by poor side effect profiles, mostly related to the vagolytic effect. Some tricyclic side effects are transitory such as a **dry mouth** and **sedation**, but others are more serious including **postural hypotension, urinary retention**, narrow angle glaucoma, paralytic ileus, and **cardiac arrhythmias**. SSRIs have safer side effect profile, have not demonstrated efficacy in the treatment of neuropathic pain. SNRIs may be effective in some forms of neuropathic pain such as diabetic neuropathy.

**Antispasmodics** A wide variety of pain conditions, both acute and chronic, may be accompanied by painful muscle spasm. Antispasmodics can be useful in treating this aspect of the patient's symptoms, but their action may be more the result of sedation rather than muscle relaxation. **Baclofen** is the most commonly used drug in this class. These medications may also **cause CNS depression** and should be used cautiously when combined with other CNS depressant medications.

**Lignocaine** The 5% lidocaine patch has shown efficacy and excellent tolerability in trials involving patients with postherpetic neuralgia and allodynia and in patients with allodynia due to different types of peripheral neuropathic pain. Lidocaine gel (5%), which is less expensive than the patch, has also shown efficacy in patients with **postherpetic neuralgia and allodynia**. Topical lidocaine is most appropriate for patients with **well localized neuropathic pain**. Although it can be used as monotherapy, it is often used as an adjunct to systemic medication.

**Substance P Depletor (Capsaicin)** is an **alkaloid derived from chili peppers**; repeated application is thought to **deplete substance P** from **primary afferent neurons**. Capsaicin is available as a cream (0.025% or 0.075%), and as a high concentration patch (8%). A systematic review found that capsaicin had moderate to poor efficacy for relief of chronic musculoskeletal or neuropathic pain, but might be useful as an adjunctive therapy or for patients unresponsive to other treatments. Capsaicin has been used in patients with post herpetic neuralgia, HIV neuropathy, and diabetic neuropathy.