sharp pain

dull aching pain

stabbing pain

nagging pain

burning pain

throbbing pain

boring pain
## Comparison of Analgesics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Narcotic (Opioids)</th>
<th>Nonnarcotic (nonopioid)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Prototype</strong></td>
<td>Morphine</td>
<td>Aspirin</td>
</tr>
<tr>
<td><strong>Pain Relieved</strong></td>
<td>Any Type</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td><strong>Site of Action</strong></td>
<td>Central</td>
<td>Peripheral and Central</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Specific Receptors</td>
<td>PG Synthesis</td>
</tr>
<tr>
<td><strong>Danger</strong></td>
<td>Tolerance &amp; Dependence</td>
<td>G.I irritation</td>
</tr>
<tr>
<td><strong>Anti-inflammatory</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Antipyretic</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Antiplatelets</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Non Narcotic Analgesics

Non Steroidal Antiinflammatory Drugs or Agents (NSAID).

Non Opioid analgesics.
NSAID

Mechanism of Action:

- **Inhibition of PG synthesis**
  - **Cyclooxygenase (COX) Enzyme:**
    - **COX-1** or Constitutional form of COX.
    - **COX-2** or Induced form of COX.
Pharmacological Actions of NSAID

- Antipyretic
- Analgesic.
- Anticoagulant.
- Antiinflammatory.
Pharmacological Actions of NSAID

- Fluid Retention
- Vasodilation
- Allergenic:
  - Bronchial Asthma
  - Anaphylaxis
- Renal Dysfunction:
  - Analgesic Nephropathy
Pharmacological Actions of NSAID

- **Gastric Irritation:**
  - Direct Irritation: with acids.
  - PG inhibition: all
  - Variable response: according to:
    - Individual,
    - Dose,
    - Agent,
    - Severity.
Pharmacological Actions of NSAID

- **Hepatic Dysfunction:**
  - Especially with acetaminophen overdose.

- **Uric Acid Excretion:**
  - Inhibited with low dose
  - Enhanced with high dose.

- **Uterine relaxation.**
Salicylates

- Weak acids: pKa 3.5
- Protein Bound.
- Distribute to all tissues
- Elimination:
  - High doses: Zero Order
  - Low doses: First Order
Figure 26–1. Structural formulas of the salicylates.
Aspirin $\xrightarrow{\text{Conjugation with glucuronic acid}}$ Ester and ether glucuronides

Sodium salicylate $\xrightarrow{\text{Conjugation with glycine}}$ Salicyluric acid

Salicylate $\xrightarrow{\text{Oxidation}}$ Gentisic acid (1%)

Acetic acid
ADRs & Overdose of Salicylates

- Hyperventilation
- Metabolic Acidosis
- Hypersensitivity: Salicylism
- Reye's Syndrome, in children.
- Bleeding
- Delayed Delivery
- Fetal Abnormalities
- Ulcerogenic
Acetaminophen = Paracetamol

- Less plasma protein bound than salicylates.
- Weak PG synthesis inhibitor
- CNS actions.
- Most widely used analgesic.
- Safest NSAID.

Munir Gharibeh, MD, PhD, MHPE
Acetaminophen = Paracetamol

- **Not:**
  - antiinflammatory
  - Platelets inhibitor
  - Ulcerogenic
  - Teratogenic
Acetaminophen = Paracetamol

- **Toxicity**
  - Severe hepatotoxicity with high doses
  - N-acetylcysteine is the antidote when given in the first 24 hours.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Postingestion Time</th>
<th>Signs and Symptoms</th>
<th>Laboratory Values</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5–24 h</td>
<td>• Nausea</td>
<td>• Subclinically elevated ALT (12 h postingestion)</td>
<td>May be asymptomatic; nonspecific symptoms may lead to further inadvertent acetaminophen administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Emesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Diaphoresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Malaise</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pallor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Compromised hydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24–72 h</td>
<td>• Right upper quadrant abdominal pain and tenderness</td>
<td>• Elevated ALT</td>
<td>Stage 1 symptoms may improve or resolve</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Midline abdominal tenderness</td>
<td>• Elevated AST</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hepatomegaly</td>
<td>• Prolonged PT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oliguria</td>
<td>• Elevated bilirubin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tachycardia</td>
<td>• Elevated BUN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypotension</td>
<td>• Elevated creatinine</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3–5 d</td>
<td>• Stage 1 symptoms</td>
<td>• Markedly elevated ALT</td>
<td>Death from multiorgan failure occurs most often in stage 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Jaundice</td>
<td>• Markedly elevated AST</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypoglycemia</td>
<td>• Elevated bilirubin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bleeding (coagulopathy)</td>
<td>• Elevated BUN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Confusion</td>
<td>• Elevated creatinine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lethargy</td>
<td>• Hyperammonemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Coma</td>
<td>• Uremia</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5–21 d</td>
<td>Eventual resolution</td>
<td>Eventual normalization</td>
<td>Complete hepatic recovery may take months</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time
Figure 26–2. Relationship of plasma levels of acetaminophen and time after acute ingestion to hepatic injury. (Adapted with permission from Rumack et al., 1981.)
Phenyacetic Acid Derivatives

- **Diclofenac:**
  - Potent, widely used.
  - Available for oral, local (ophthalmic, topical gel), mouth wash, rectal and parenteral administration (for renal colic).
Propionic Acid Derivatives

- Ibuprofen
- Ketoprofen
- Naproxin
Older Analgesics

- **Indomethacin**
  - Pancytopenia
- **Phenylbutazone**
  - Aplastic Anemia
- **Mefenamic Acid**
Cyclooxygenase II Inhibitors

- Meloxicam
- Rofecoxib
- Celocoxib
Figure 26-4. Chemical structures of the coxibs.
Cyclooxygenase II Inhibitors

- Do not affect platelet function.
- Less gastroirritant (half of non-selective drugs).
- May increase the incidence of edema and hypertension.
- Higher incidence of cardiovascular thrombotic events.
- Can cause renal toxicity like other NSAIDs.
Disease -Modifying Antirheumatic Drugs “DMARDs”

- Rheumatoid arthritis is a chronic immunologic disease that causes significant systemic debilitating effects, shortens life, and reduces mobility and quality of life.
- DMARDs might arrest, or at least slow the progression of rheumatoid arthritis by modifying the disease itself.
- These drugs need weeks or months to work.

- **Nonbiologic:**
  - Mostly synthetic or semisynthetic.

- **Biologics:**
  - Usually monoclonal antibody
Disease -Modifying Antirheumatic Drugs “DMARDs”

- **Nonbiologic:**
  - Hydroxychloroquine.
  - Thalidomide.
  - Sulfasalazine.
  - Azathioprine.
  - Cyclosporin.
  - Methotrexate.
  - Sulfasalazine.
  - Gold Salts.
Disease - Modifying Antirheumatic Drugs “DMARDs”

- **Nonbiologic:**

- **Biologics:**
  - Abatacept
  - Adalimumab.
  - Infliximab.
  - Etanercept.
FIGURE 36-4 Structures of TNF-α antagonists used in rheumatoid arthritis. $C_H$, constant heavy chain; $C_L$, constant light chain; $F_o$, complex immunoglobulin region; $V_H$, variable heavy chain; $V_L$, variable light chain. Red regions, human derived; blue regions, mouse derived.
FIGURE 36–5 Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. PG, prostaglandin; IL-1, interleukin-1; LTB₄, leukotriene B₄.
Colchicine

- Was the primary treatment for acute gout, but nowadays, NSAIDs are the first-line drugs.

- Also effective in Mediterranean fever.

- Rapidly absorbed, and rapidly effective (12-24 hr.).

- Works on tubulin and prevents its polymerization, leading to inhibition of leukocyte migration, phagocytosis, and leukotriene B4 formation.
Colchicine

- **Adverse Effects:**
  - Diarrhea, could be very severe and bloody.
  - N,V, abdominal pain.
  - Many other side effects (hepatic necrosis, renal failure, coagulation, seizures etc...).
  - Severe effects appeared with intravenous treatment.
  - NSAIDs are used instead of cholchicine to avoid these side effects.
NSAIDs

- All NSAIDs can be used in acute cases.
- Indomethacin, an old NSAID is very effective.
- However, aspirin in low doses can cause uric acid retention.
Uricosuric Agents

- **Probenecid**
- **Sulfinpyrazone**

  - Employed to decrease levels of urate in the body, or in patients with frequent attacks.
  - Act on the renal acid secretory mechanism to prevent reabsorption of uric acid.
  - Renal stone formation might be augmented, so urine volume should be increased with alkalinazation.
Allopurinol

- Xanthine oxidase inhibitor.
- Results in a fall in urate level.
- First line drugs for the treatment of chronic gout between the attacks.
- Started after NSAIDs.
- N, V, D, neuritis, bone marrow suppression, allergies, cataracts, .....etc.