Drugs Acting On Central Nervous System

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are a cornerstone in pain management and are widely used for their:

- **Analgesic** (pain relief)
- **Antipyretic** (fever reduction)
- **Anti-inflammatory** effects

They are considered **non-opioid analgesics**, often referred to as **aspirin-like drugs**, and are used extensively for minor to moderate pain, fever, and inflammatory conditions.

? Classification of Analgesics

1. **Opioid Analgesics** – act on CNS opioid receptors (e.g., morphine)
2. **Non-Opioid Analgesics** – include NSAIDs and acetaminophen (paracetamol)

? Classification of NSAIDs

1. **Salicylates** – e.g., Aspirin
2. **Para-aminophenol derivatives** – e.g., Paracetamol (Acetaminophen)
3. **Non-selective COX inhibitors** – e.g., Ibuprofen, Diclofenac, Naproxen
4. **Selective COX-2 inhibitors** – e.g., Celecoxib, Etoricoxib

? Mechanism of Action

NSAIDs inhibit the **cyclooxygenase (COX)** enzymes involved in **prostaglandin synthesis**:

- **COX-1**: Constitutive; protects gastric mucosa, supports platelets & renal function
- **COX-2**: Inducible; mediates inflammation, pain, and fever

Most NSAIDs inhibit both COX-1 and COX-2 ? ? Prostaglandins ? ? pain, inflammation, fever
?? **Side effect**: Gastric ulceration due to COX-1 inhibition
?? **Solution**: **Selective COX-2 inhibitors** reduce GI toxicity

? Detailed Drug Profiles

? 1. Salicylates (Aspirin / Acetylsalicylic Acid)

Pharmacokinetics:

- Administered **orally**, absorbed in stomach/small intestine
- Converted to active **salicylate** in the **liver** (prodrug)
- Plasma protein binding increases with dose

Mechanism:

- **Irreversible inhibition** of COX-1 & COX-2
- **Antipyretic**: Acts on hypothalamus to reset thermoregulation
- **Analgesic & anti-inflammatory**: Reduces prostaglandin-mediated inflammation

Therapeutic Uses:

- **Mild pain & inflammation** (e.g. arthritis)
- **Fever** control
- **Cardioprotection**: Low-dose aspirin inhibits **platelet aggregation** by blocking thromboxane A2 (TXA2)

Adverse Effects:

- GI: Nausea, epigastric pain, ulceration
- **Salicylism** (toxicity): tinnitus, vertigo, hyperventilation, confusion
- **Reye's Syndrome**: Avoid in children with viral infections
- **Hypersensitivity**: Asthma, rash
- **Bleeding risk**
- **Acute overdose**: Metabolic acidosis, convulsions, coma

Treatment of Overdose:

- **Supportive care**: IV fluids, temperature control
- **Gastric lavage**, **activated charcoal**
- **Alkaline diuresis** to enhance salicylate elimination
- **Vitamin K** if bleeding
- **Hemodialysis** in severe cases

Contraindications:

- Peptic ulcer disease, bleeding disorders, asthma, liver disease, pregnancy (especially 3rd trimester)

? 2. Paracetamol (Acetaminophen)

Mechanism:

- Weak COX inhibitor, mainly in **CNS**
- **No significant anti-inflammatory action**
- **Does not affect platelet function**

Therapeutic Uses:

- **Antipyretic and mild analgesic**
- Preferred for **children**, elderly, and **gastric-sensitive** patients

Advantages:

- No gastric irritation
- No effect on clotting or uric acid levels
- No risk of Reye's syndrome

Adverse Effects:

- Generally safe at therapeutic doses
- **Overdose risk**: Hepatotoxicity due to formation of toxic metabolite (**NAPQI**) that depletes glutathione

Treatment of Overdose:

- **Activated charcoal** (within 1–2 hours)
- **N-acetylcysteine (NAC)**: Replenishes glutathione, prevents liver damage

? 3. Common NSAID Combinations

Often, **aspirin or paracetamol** is combined with weak opioids (e.g., **codeine**) to manage **moderate pain** without significant addiction risk:

- Paracetamol + Codeine
- Aspirin + Codeine

? NSAIDs and Uterine Contraction

- **Prostaglandins** promote uterine contractions during menstruation and labor
- NSAIDs (especially mefenamic acid, ibuprofen) are used for **dysmenorrhea** and to delay **preterm labor** (e.g., **indomethacin**)

? Older NSAIDs

Indomethacin

- Powerful NSAID used in **rheumatic diseases** and **gout**
- Can cause **CNS and GI side effects**
- Also used to close **patent ductus arteriosus** in neonates

Phenylbutazone

- Potent anti-inflammatory but now rarely used due to serious side effects: **agranulocytosis**, **gastric ulcers**

? Commonly Used Non-Selective NSAIDs

Drug	Notes
Ibuprofen	Good safety profile, OTC
Diclofenac	Used in arthritis, available as suppository/injection

Drug	Notes
Naproxen	Long half-life
Ketoprofen	Rapid onset
Aceclofenac	Better GI tolerance
Piroxicam	Long-acting, once daily dosing
Meloxicam	Preferential COX-2 inhibitor, better GI safety

?? Use **lowest effective dose** for shortest duration
?? Rotate if ineffective after **2–3 weeks**

? Selective COX-2 Inhibitors (Coxibs)

Drug	Notes
Celecoxib	Effective for arthritis, lower GI toxicity
Etoricoxib	Long-acting, used in osteoarthritis & gout

May increase **cardiovascular risk** (MI, stroke)

?? General Side Effects of NSAIDs

- **Gastrointestinal**: Ulcers, bleeding, nausea
- **Renal**: ? renal perfusion ? fluid retention, hypertension, acute kidney injury
- **Cardiovascular**: Risk of MI and stroke (especially with COX-2 inhibitors)
- **Hematologic**: Platelet inhibition (esp. aspirin)
- **Hypersensitivity**: Asthma, rash, anaphylaxis

? High-Yield Clinical Pearls

- **Aspirin is irreversible COX inhibitor** ? unique antiplatelet effect
- **Avoid aspirin in children with viral illness** ? Reye's syndrome risk
- **Paracetamol overdose** ? hepatotoxicity due to **NAPQI**, treat with **N-acetylcysteine**
- **NSAIDs may mask infection symptoms** (fever and pain)
- Use **proton pump inhibitors (PPIs)** with chronic NSAID therapy in GI-risk patients
- **Ibuprofen is safest among OTC NSAIDs** for mild-moderate pain

? Suggested Exam Questions Focus

- Mechanism of action of NSAIDs and COX inhibition
- Aspirin vs. acetaminophen (clinical use & toxicity)
- Management of overdose (salicylate & paracetamol)
- NSAIDs effect on kidney and GI tract
- COX-2 inhibitors and cardiovascular risks