
بسم الله الرحمن الرحيم

Non-Steroidal Anti-inflammatory Drugs

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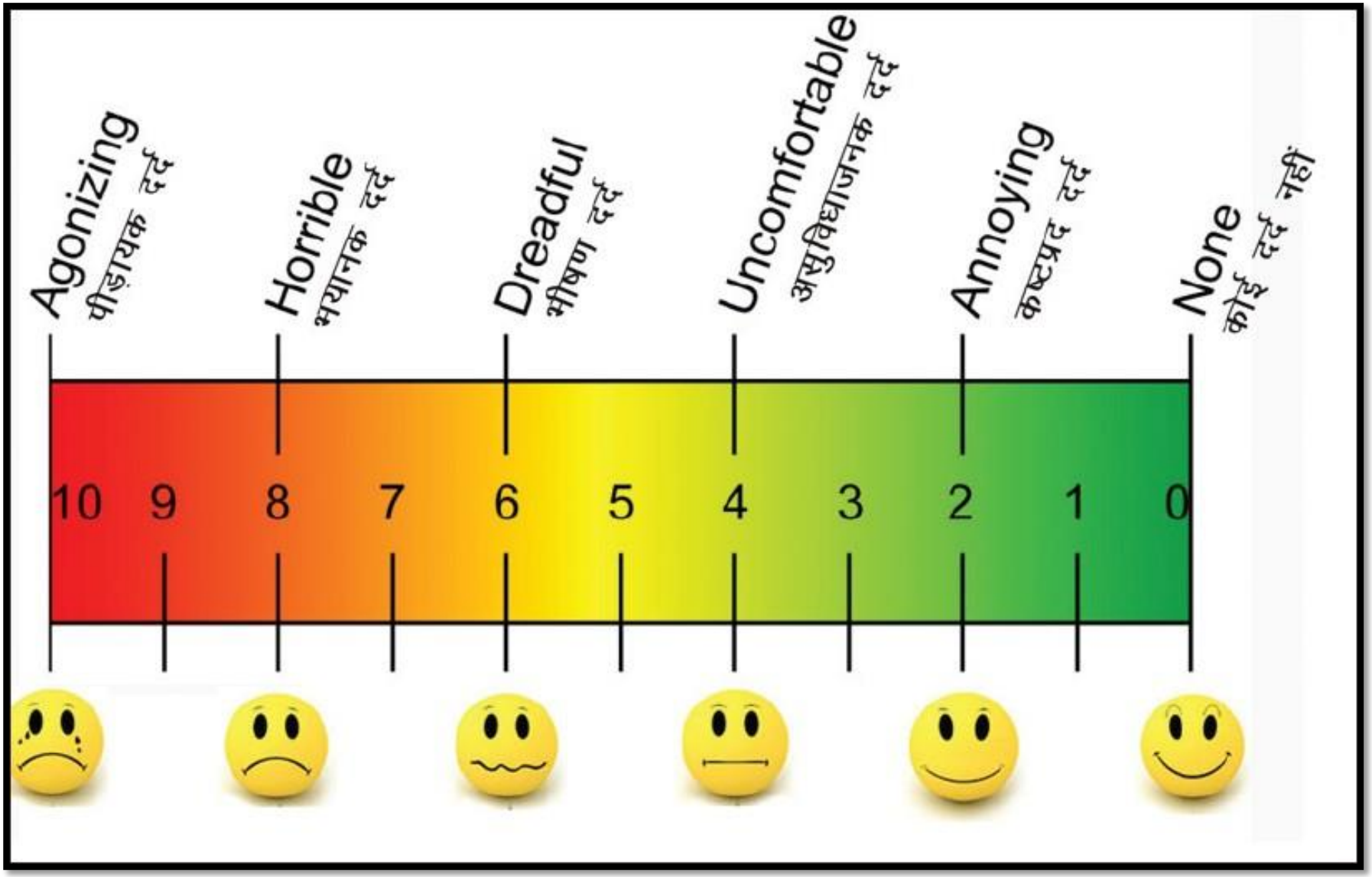
Pain management

- **Pain classification**
  - **It is divided into acute and chronic**
  - **It is divided into nociceptive and neuropathic**

- **Pain intensity scales**
  - **Showing a diagram to the patient and asking the patient to indicate the appropriate rating.**
  - **Used by simply asking the patient for a verbal response**


Agonizing
पीड़ायक दर्द
Horrible
भयानक दर्द
Dreadful
भीषण दर्द
Uncomfortable
असुविधाजनक दर्द
Annoying
कष्टप्रद दर्द
None
कोई दर्द नहीं
10 9 8 7 6 5 4 3 2 1 0

Important considerations

- Pain is a subjective phenomenon
- Pain threshold and tolerance and analgesic requirements vary widely among patients
- Response to analgesic agents is a subjective phenomenon

There are some misconceptions regarding use of analgesics

- **Patients who are in pain always have observable signs**
- **Obvious pathology, test results, and the type of surgery determine the existence and the intensity of pain**
- **Patients should wait as long as possible before taking a pain medication because this period of abstinence teaches them to have a better tolerance for pain**

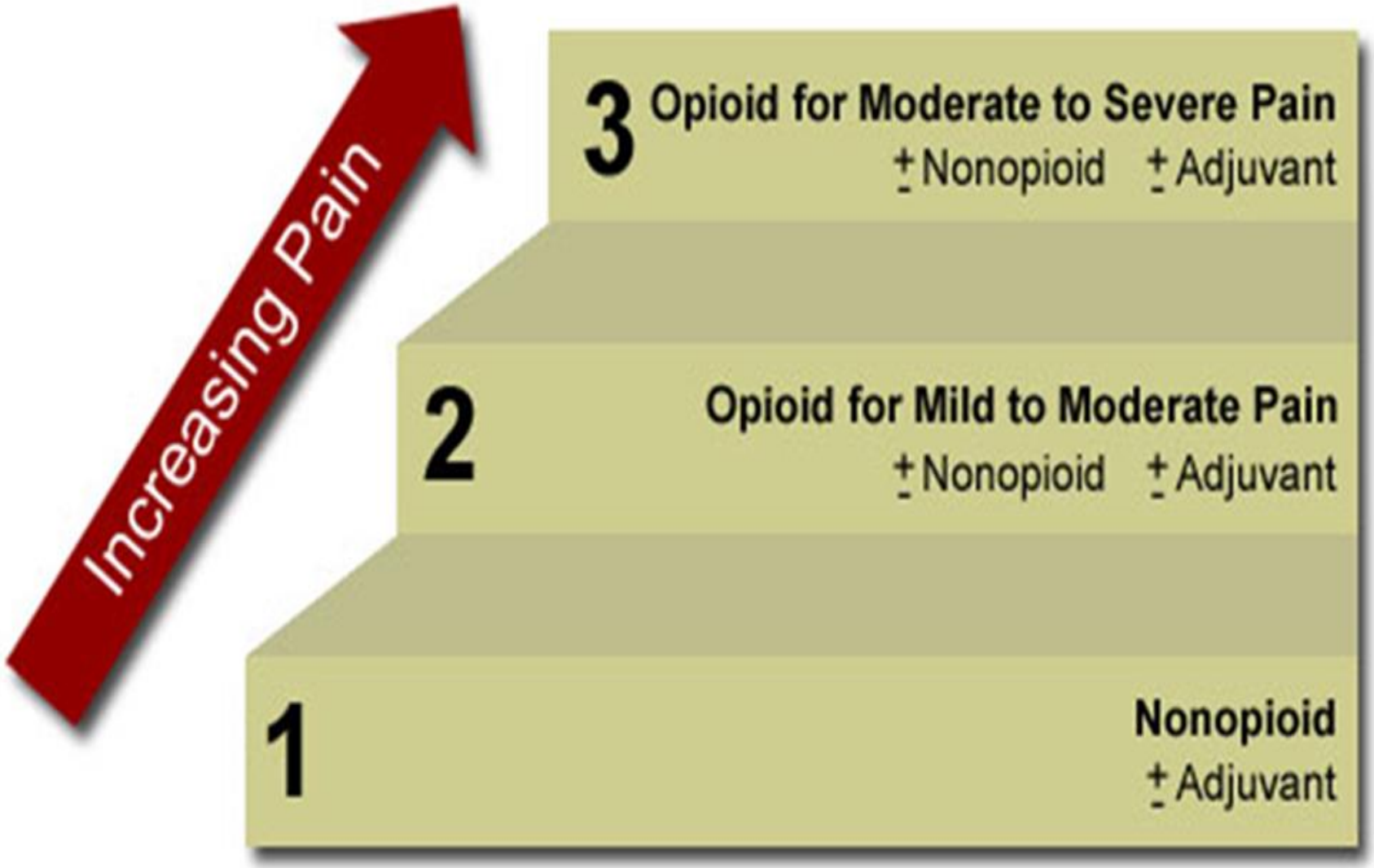
Levels of pain generation

Pharmacologic control of pain is classified at three processes:

- **Initiation of impulses**
  - **NSAIDs**
- **Propagation of the impulses**
  - **Local anesthetics**
- **Perception of painful stimuli**
  - **Opioids**

Factors affecting analgesic selection:

- **Cause of Pain intensity**
- **Pain severity**
- **History of response to analgesic agents**


Increasing Pain
3
Opioid for Moderate to Severe Pain
±Nonopioid ±Adjuvant
2
Opioid for Mild to Moderate Pain
±Nonopioid ±Adjuvant
1
Nonopioid
±Adjuvant

Opioid vs. non-opioid analgesics

Non-opioid analgesic agents

Overview:

- ❑ **Non-steroidal Anti-Inflammatory Drugs (NSAIDs)**
- ❑ **Selective COX-2 inhibitors**
- ❑ **Acetaminophen**

Properties:

- **Analgesic (CNS and peripheral effect) may involve non-PG related effects**
- **Antipyretic (CNS effect)**
- **Anti-inflammatory (except acetaminophen) due mainly to PG inhibition**

NSAIDs Vs Opioids

Nonsteroidal Anti inflammatory Drugs (Aspirin)	Opioids (Example-Morphine, Methadone)
Weaker Analgesic	Strong Analgesic
Acts Peripherally	Acts both Spinal and Supraspinal (emotional)
Do not depress CNS	Depress CNS (sedation, euphoria)
No abuse liability	High abuse potential
No dependence	Can Cause Physical and Mental Dependence

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

2. Mechanism of action: inhibition of the inflammatory response

a. Normal inflammatory response

- series of events that aid our survival in response to injury

b. Mediated by a host of endogenous compounds

-Histamine

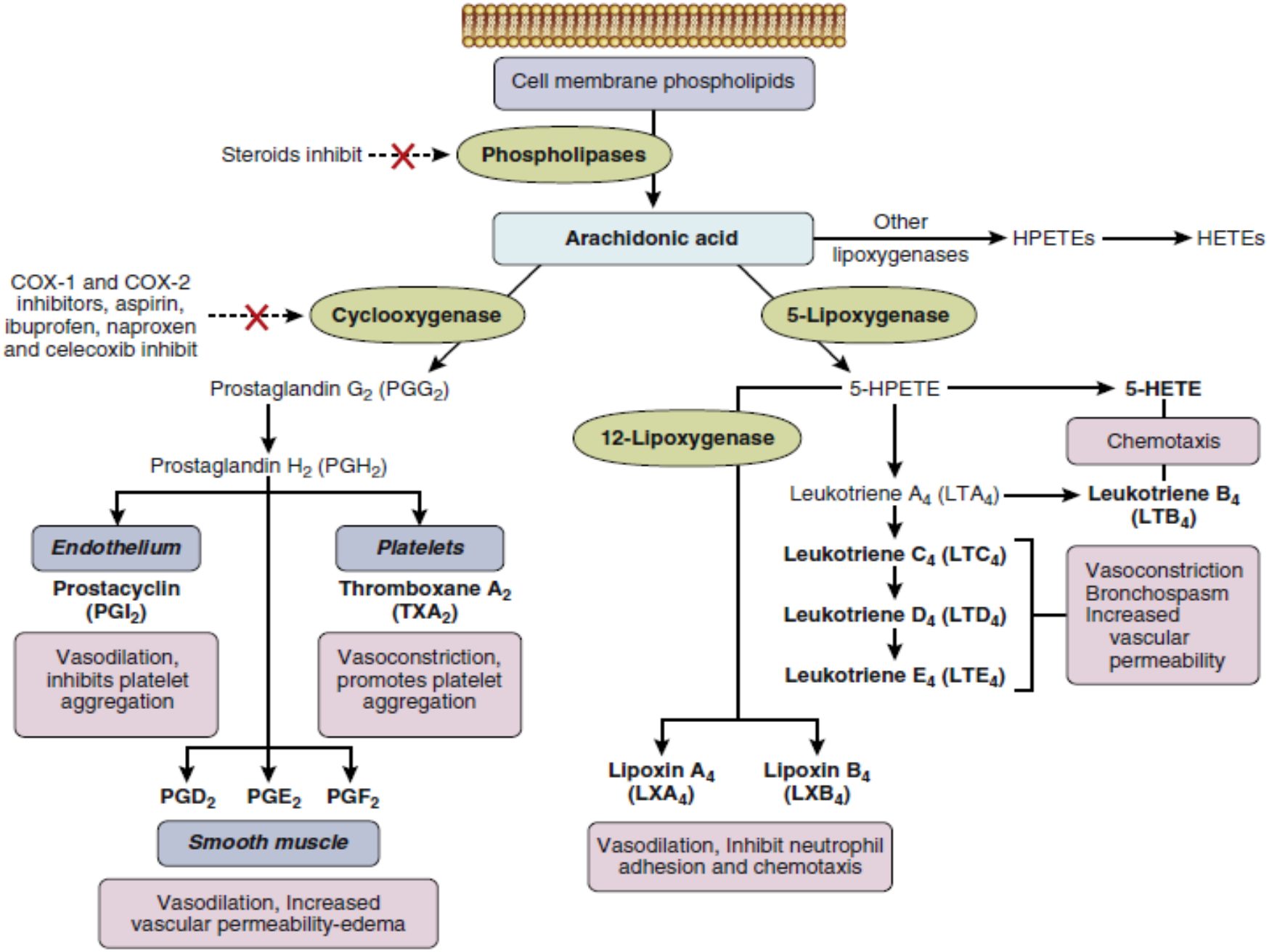
-Serotonin

-Complement

-Bradykinin

-Prostaglandins (PGs)

-Leukotrienes (PLs)


Cell membrane phospholipids
Steroids inhibit
Phospholipases
Arachidonic acid
Other lipoxygenases
HPETEs
HETEs
COX-1 and COX-2 inhibitors, aspirin, ibuprofen, naproxen and celecoxib inhibit
Cyclooxygenase
5-Lipoxygenase
Prostaglandin G2 (PGG2)
Prostaglandin H2 (PGH2)
5-HPETE
5-HETE
12-Lipoxygenase
Chemotaxis
Leukotriene A4 (LTA4)
Leukotriene B4 (LTB4)
Endothelium
Prostacyclin (PGI2)
Vasodilation, inhibits platelet aggregation
Platelets
Thromboxane A2 (TXA2)
Vasoconstriction, promotes platelet aggregation
Leukotriene C4 (LTC4)
Leukotriene D4 (LTD4)
Leukotriene E4 (LTE4)
Vasoconstriction Bronchospasm Increased vascular permeability
PGD2
PGE2
PGF2
Smooth muscle
Vasodilation, Increased vascular permeability-edema
Lipoxin A4 (LXA4)
Lipoxin B4 (LXB4)
Vasodilation, Inhibit neutrophil adhesion and chemotaxis

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Prostaglandins act (among other things) as messenger molecules in the process of inflammation
- COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes.
- One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid.
- COX-2 is an inducible enzyme facultative expressed in inflammation.

Two main forms of Cyclooxygenases (COX)

- **Cyclooxygenase-1 (COX-1)**

- Produces prostaglandins that mediate homeostatic functions
- Constitutively expressed
- Inhibit **PGE1** synthesis which has important role in GI
- Plays an important role in
  - Gastric mucosa
  - Kidney
  - Vascular endothelium

- **Cyclooxygenase-2 (COX-2)**

- Produces prostaglandins that mediate inflammation, pain, and fever.
- Induced mainly in sites of inflammation by cytokines
- Inhibit **PGI2** synthesis which has important role in platelet function

Classification of NSAID'S

- **Non selective NSAID's**
- **Diclofenac**
- **Ibuprofen**
- **Ketoprofen**
- **Aspirine**
- **Naproxen**
- **Piroxlcam**
- **Indomethacin**

Preferential SELECTIVE NSAID's

Meloxicam

SELECTIVE NSAID's

Celecoxib
Rofecoxib
Etoricoxib

CHEMICAL CLASSIFICATION OF NSAID'S

1) Alicylates

- Aspirin
- Salicylic acid

2)Propionic acid derivatives

- Ibuprofen
- Naproxen
- Ketoprofen

3)Acetic acid derivatives

- Tolmetin
- Diclofenac

4)Selective COX-2 inhibitors

- Celecoxib
- Rofecoxib
- Valdecoxib

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

COX-2 Inhibitors

- **The rationale behind development of these drugs was that:**
  A. **inhibition of COX-2 would reduce the inflammatory response and pain**
  B. **not inhibit the cytoprotective action of prostaglandins in the stomach, which is largely mediated by COX-1.**

- **Rofecoxib and valdecoxib have been removed from the market due to a doubling in the incidence of heart attack and stroke**

- **Celecoxib remains on the market and is approved for:**
  - **Osteoarthritis and rheumatoid arthritis**
  - **Pain including bone pain, dental pain, and headache**
  - **Ankylosing spondylitis.**

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
COX-2 Inhibitors

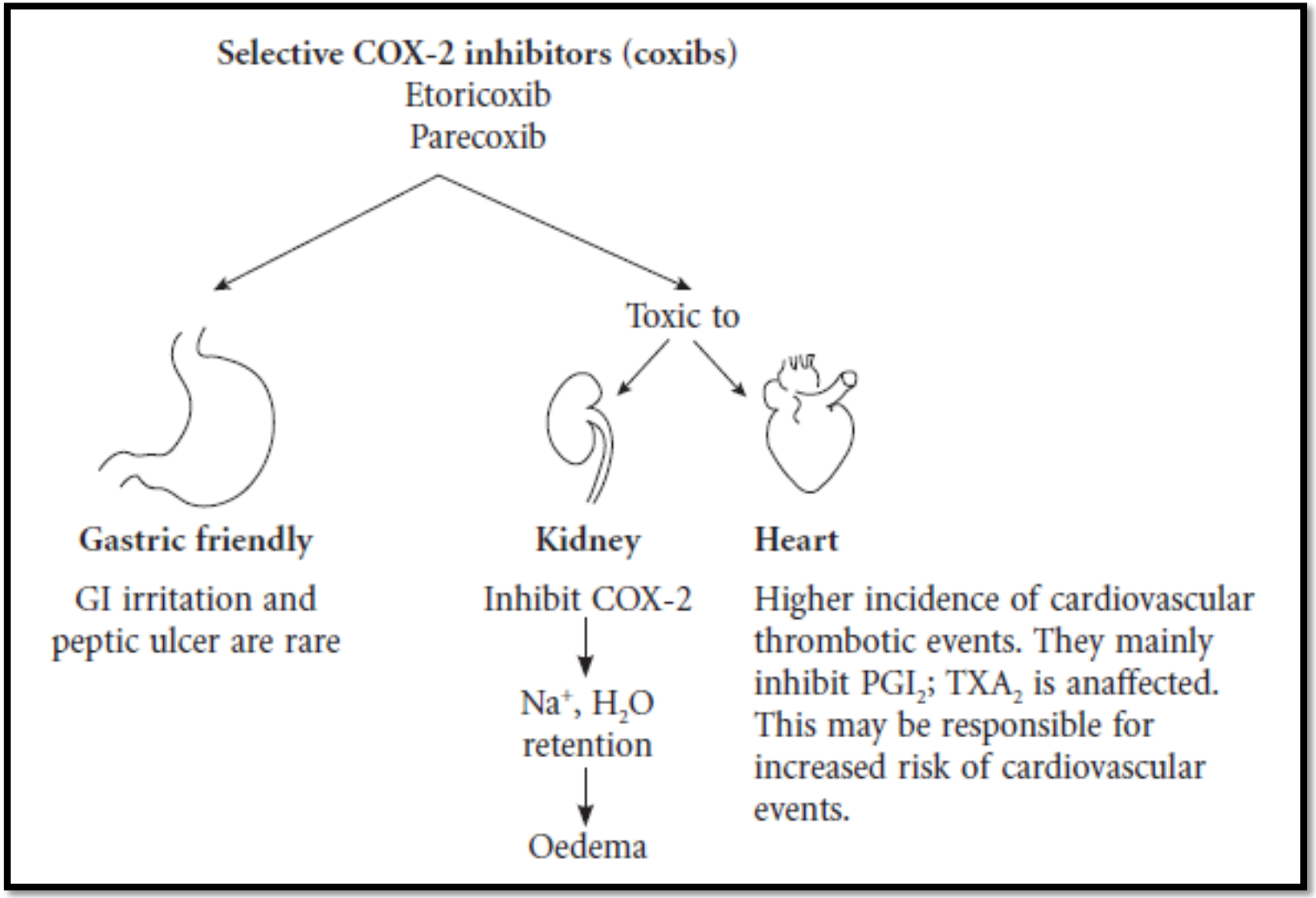


Table 7.4 Differences Between Nonselective COX and Selective COX-2 Inhibitors

Nonselective COX Inhibitors	Selective COX-2 Inhibitors
Analgesic effect +	Analgesic effect +
Antipyretic effect +	Antipyretic effect +
Antiinflammatory effect +	Antiinflammatory effect +
Antiplatelet effect +	No antiplatelet effect
GI side effects are marked + +	GI side effects are less (less ulcerogenic potential)
Renal toxicity + (sodium and water retention)	Renal toxicity +

+: present; ++: effect is more.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

1. Antiinflammatory effect

- **Anti-inflammatory (except acetaminophen) due mainly to PG inhibition.**
- **Some shown to inhibit activation, aggregation, adhesion of neutrophils & release of lysosomal enzymes**

2. Analgesic effect

The analgesic effect of NSAIDs is thought to be related to:

- the **peripheral inhibition of PG production**
- **Analgesic may involve non-PG related effects**
- due to the inhibition of pain stimuli at a **subcortical site**.
- **NSAIDs prevent the potentiating action of prostaglandins on endogenous mediators of peripheral nerve stimulation (e.g., bradykinin).**

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

3. Antipyretic effect

- The antipyretic effect of NSAIDs is believed to be related to:
  - **Antipyretic (CNS effect)**
  - **Inhibition of production of prostaglandins induced by interleukin-1 (IL-1) and interleukin-6 (IL-6) in the hypothalamus**
  - **The "resetting" of the thermoregulatory system**, leading to **vasodilatation and increased heat loss.**

4. Some are Uricosuric

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Clinical indications:

- Differences with opioids?
- Dose-related indications
  - Low doses: Antipyretic and analgesic effect
  - High doses: Anti-inflammatory effects

- NSAIDS are not main treatment
- NSAIDS are not effective on disease progression
- Patient's risk factor should be carefully considered
- NSAIDS are <u>not effective on all kind of inflammatory disease</u>
- In some Inflammatory disease NSAIDS are contraindicated

Therapeutic uses

1. Inflammation

- **NSAIDs are first-line drugs used to arrest inflammation and the accompanying pain of rheumatic and nonrheumatic diseases, including:**
  - **Rheumatoid arthritis**
  - **Juvenile arthritis**
  - **Osteoarthritis**
  - **Psoriatic arthritis**
  - **Ankylosing spondylitis**
  - **Bursitis and tendonitis**
  - **Ocular inflammation**
  - **Irritable bowl syndrome and crohn's disease**
  - **Gout**

❑ **In this indication, Dose, duration and also side effects of NSAIDS is more higher compared to analgesic and antipyretic effects**

Therapeutic uses

2. Analgesia

- **NSAIDs alleviate mild-to-moderate pain** by:
  - decreasing PGE- and PGF-mediated increases in pain receptor sensitivity.
- **Myalgia**
- **Arthritis**
- **Bursitis**
- **Visceral pain**

3. Antipyresis

- NSAIDs **reduce elevated body temperature** with little effect on normal body temperature.

Therapeutic uses

Other indications

- Antithrombotic effect
  - Only ASA is used
- Gout
- Closure of ductus arteriosus (indomethacin is preferred)

  [PGE2 leads to dilation (opening) of ductus arteriosus]
- Inflammatory bowl disease
  - 5-Amino salicylates (mesalamine, sulfasalazine)

- Salicylic acid is used topically to treat:
  - Plantar warts
  - fungal infections
  - Corns

Therapeutic uses

Important information

- Drug dosage forms
  - Oral
  - Rectal
  - injection
  - Topical
- Oral preferred; rectal used on some cases
- Most of the time, food could not affect drug GI absorption
- recommended to use after meal except:
  - Diclofenac
  - Tolmetin

Table 7.3 NSAIDs and Their Important Features

Drug	Route and Formulations with Oral Dose	Other Points
1. Ibuprofen	Oral and topical gel Dose: 400–600 mg TDS	• It has moderate antiinflammatory effect • It is better-tolerated than aspirin • It can be used in children (does not cause Reye's syndrome)
2. Diclofenac	Oral, i.m., rectal, topical, gel and ophthalmic preparation (eye drops) Dose: 50 mg BD or 100 mg sustained-release preparation OD	• It has potent antiinflammatory effect • It gets concentrated in synovial fluid, hence preferred in inflammatory conditions of joint (arthritis) • Incidence of hepatotoxicity is more • Combination of diclofenac with misoprostol (PGE_1 analogue) available, which reduces GI irritation and peptic ulcer
3. Indomethacin Note: It has • *extra* mechanism • *extra* uses • *extra* side effects	Oral, eyedrops and suppository Dose: 50 mg TDS	• It is a nonselective COX inhibitor • It has potent antiinflammatory effect • It inhibits migration of neutrophils to inflamed area • It is very effective in ankylosing spondylitis, acute gout and psoriatic arthritis • It has prominent GI side effects • CNS side effects are severe headache, confusion, hallucinations, etc. • It is contraindicated in epileptics, psychiatric patients and drivers
4. Piroxicam	Oral, i.m. and topical gel Dose: 20 mg OD	• It has potent antiinflammatory effect • It is long-acting • Increased incidence of peptic ulcer and bleeding
5. Ketorolac	Oral, i.m., i.v., ophthalmic preparation and transdermal patch Dose: 10–20 mg QID	• It has potent analgesic effect and efficacy is almost equal to morphine. • It relieves pain without causing respiratory depression, hypotension and drug dependence • It is used in renal colic, postoperative and metastatic cancer pain
6. Mefenamic acid	Oral Dose: 250–500 mg TID	• It has analgesic , antipyretic and weak antiinflammatory effect • It is used in dysmenorrhoea, osteoarthritis, rheumatoid arthritis

Therapeutic uses

Important information

- **About ASA: zeorder metabolism in high doses**
  - Increases the HL to 15—30 hours because the enzymes for **glycine and glucuronide conjugation become saturated.**

Aspirin per se is rarely used at present because of the following disadvantages

- **It has a short duration of action, requires large doses and frequent administration**
- **Gastric irritation and ulcerogenic effect is high with aspirin.**
- **Salicylates should be avoided in children with viral infection.**
- **NSAIDs may precipitate bronchospasm in patients with bronchial asthma (aspirin-induced asthma)**

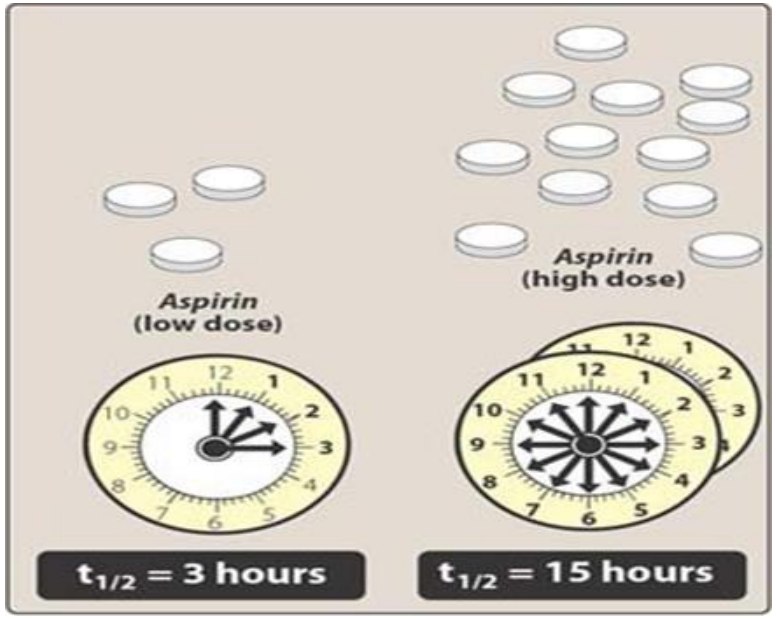


TABLE 17-3 Potential Contraindications to the Use of Aspirin and Other Salicylates

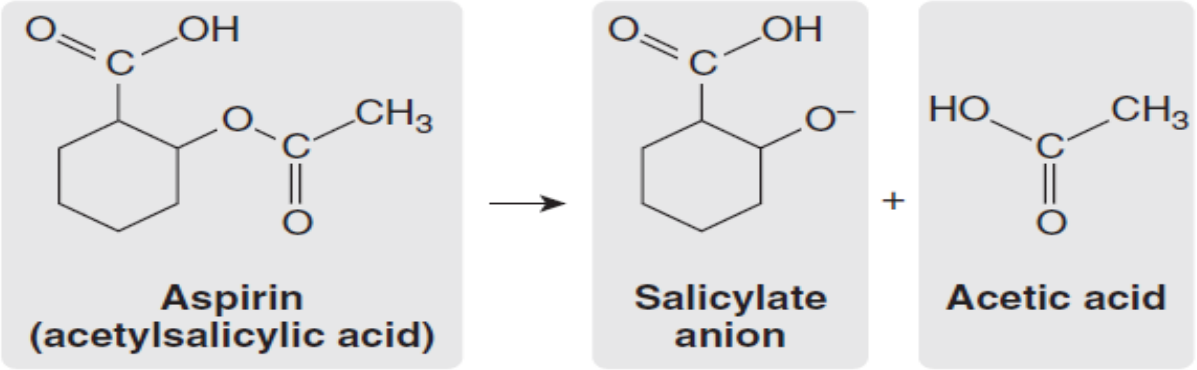
Disease State	Possible Adverse Effect of Aspirin
Ulcer	Internal bleeding, possible hemorrhaging
Asthma	Asthmatic attack resembling an allergic reaction
Diabetes	High doses may cause hyperglycemia or hypoglycemia
Gout	Low doses increase plasma urate; high doses lower plasma urate
Influenza, varicella, and other viral conditions	Reye's syndrome in children
Hypocoagulation	Excessive bleeding states

Important information

Aspirin

- Analgesic dose: 2–3 g/day in divided doses
- Antiinflammatory dose: 4–6 g/day in divided doses
- Antiplatelet dose: 50–325 mg/day (**low-dose aspirin**)

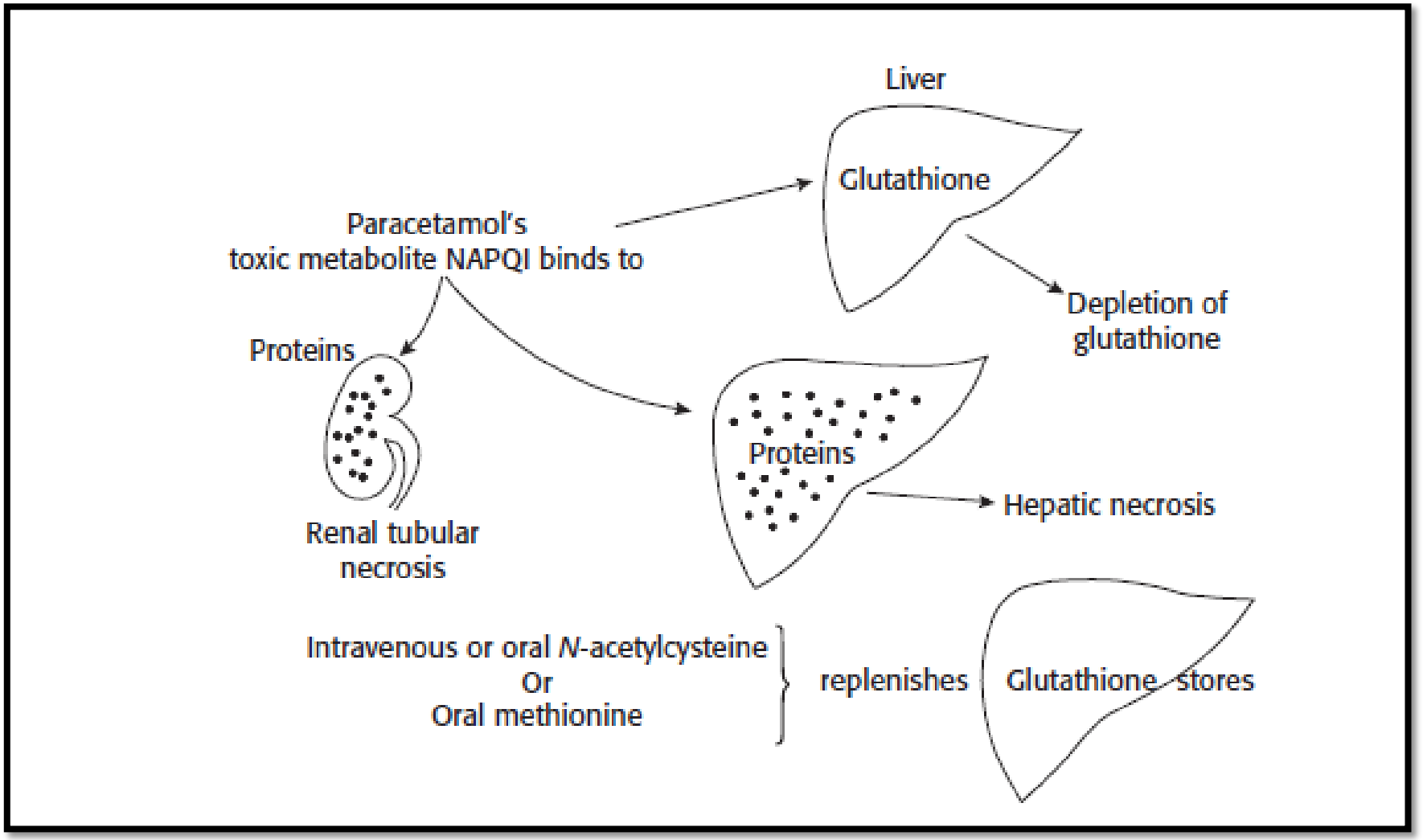
The majority of platelet COX acetylation may occur pre-systemically as platelets pass through gut capillaries before the hydrolysis of aspirin to salicylate



Important information

- **Acetaminophen (paracetamol)**
  - Is not a real NSAID
  - No anti-inflammatory activity
  - Has No effect on platelet adhesion an aggregation
  - Has both central and peripheral analgesic effects
  - Overdose (> 4gr), could lead to hepatotoxicity
  - Nephrotoxicity is commonly seen on chronic use.
- **Mechanism of toxicity and treatment:**
  - High doses cause depletion of glutathione levels
  - In the absence of glutathione, toxic metabolite binds covalently with proteins in the liver and kidney and causes necrosis
  - Alcoholics and premature infants are more prone to hepatotoxicity
  - N-acetylcysteine or oral methionine replenishes the glutathione stores of liver

Acetaminophen-induced hepatotoxicity



Therapeutic uses

Important information

- **Acetaminophen is a substitute for aspirin to treat mild-to-moderate pain for selected patients who are:**
  - **Intolerant to aspirin**
  - **Have a history of peptic ulcer or hemophilia**
  - **Are using anticoagulants or a uricosuric drug to manage gout**
  - **Are at risk for reye's syndrome.**
  - **Asthma history**

Therapeutic uses

Important information

Table 7.5 **Differences Between Aspirin and Paracetamol**

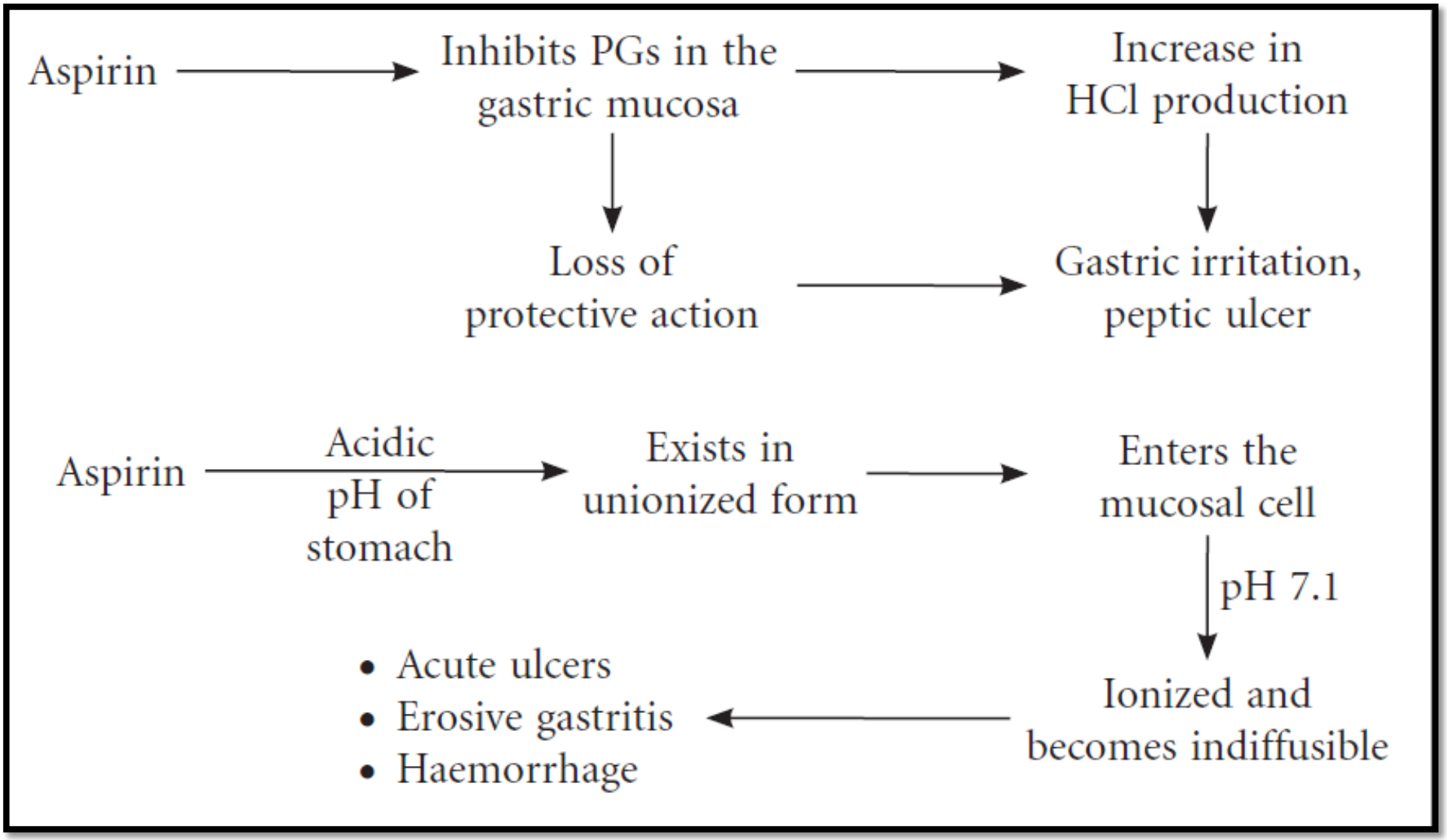
Aspirin	Paracetamol
1. It is a salicylate derivative	1. It is a *para*-aminophenol derivative
2. It has analgesic, antipyretic and potent antiinflammatory effects	2. It has potent antipyretic and analgesic effects with poor antiinflammatory activity
3. It causes GI irritation (nausea, vomiting, peptic ulcer and bleeding)	3. It usually does not produce gastric irritation
4. In large doses, it produces acid–base and electrolyte imbalance	4. It does not produce acid–base and electrolyte imbalance
5. It has antiplatelet action	5. It has no antiplatelet action
6. It has no specific antidote	6. *N*-acetylcysteine is the antidote
7. It is contraindicated in peptic ulcer, people with bleeding tendency, bronchial asthma and in children with viral infection	7. Paracetamol is the preferred analgesic and antipyretic in patients having peptic ulcer, bronchial asthma and in children

NSAIDS's Side effects

- **GI complications range:**
  - Most common adverse effects of high-dose **aspirin** use (70% of patients):
    - **Nausea**
    - **Vomiting**
    - **Diarrhea or constipation**
    - **Dyspepsia (impaired digestion)**
    - **Reflux**
    - **Gastric pain**
    - **GI ulceration**
    - **GI bleeding**

- **mechanisms of GI ulceration:**
  - **Direct action**
  - **Indirect action (PG-dependent)**

Mechanism of ASA GI irritation



NSAIDS's Side effects

- **High risk patients to GI bleeding of NSAIDS:**
  - Age over 65
  - History of GI ulceration
  - NSAID intolerance
  - Cigarette smoking
  - Alcoholism

GI side effect management

- Use enteric-coated tables
- Use of non-salicylate NSAIDs
- After meal administration
- Omeprazole co-administration
- Antacid co-administration
- Misoprostol co-administration

NSAIDS's Side effects

❑ Hypersensitivity (intolerance)

- **Hypersensitivity is relatively uncommon with the use of aspirin (0.3% of patients); hypersensitivity results in:**
  - **❑ Rash**
  - **❑ Bronchospasm**
  - **❑ Rhinitis**
  - **❑ Edema**
  - **❑An anaphylactic reaction with shock**

❑ The incidence of intolerance is highest in patients with asthma, nasal polyps, recurrent rhinitis, or urticaria.

- **Cross-hypersensitivity** may exist:
  - **to other NSAIDs**
  - **to the yellow dye tartrazine**
- **Aspirin should be avoided in such patients.**

NSAIDS's Side effects

❑ Hypersensitivity (intolerance)

The use of aspirin and other salicylates to control fever during viral infections (influenza and chickenpox) in children and adolescents is associated with an increased incidence of Reye's syndrome, an illness characterized by:

- **Vomiting**
- **Hepatic disturbances**
- **Encephalopathy that has a 35% mortality rate.**

- **Acetaminophen is recommended as a substitute for children with fever of unknown etiology.**

NSAIDS's Side effects

Aspirin Toxicity

- In adults, **salicylism** (tinnitus, hearing loss, vertigo) occurs as initial sign of toxicity after **aspirin** or **salicylate** **overdose** or poisoning.
- In children, the common signs of toxicity include **hyperventilation** and **acidosis**, with accompanying lethargy and hyperventilation.

Treatment of Aspirin Toxicity includes:

- ❑ **Gastric lavage by activated charcoal (physical antagonist)**
- ❑ **Correction of acid—base disturbances**
- ❑ **Replacement of electrolytes and fluids**
- ❑ **External cooling**
- ❑ **Intravenous sodium bicarbonate to treat metabolic acidosis**
- ❑ **Alkalization of urine with bicarbonate**
- ❑ **Forced diuresis, hemodialysis (sever cases)**
- ❑ **Vitamin K1 and blood transfusion, if there is bleeding**

NSAIDS's Side effects

- **Cardiovascular side effects:**
  - **Hypertension**
  - **Therombosis**
  - **Bleeding**
  - **Myocardial infaction**
- **This complication is higher in COX2 inhibitors**
  - **Warning notice on drug box**
  - **Contraindicated in thrombotic cases**

- **Salicylates are not recommended during pregnancy; they may induce:**
  - **postpartum hemorrhage**
  - **premature closure** of the **fetal ductus arteriosus**

NSAIDS's Side effects

- Renal side effects
  - Indirect action due to PG synthesis inhibition:
    - renal artery vasoconstriction
    - decrease GFR
    - Decrease urine volume
    - Increased plasma volume
    - Edema and rapid wait gain
  - Direct nephrotoxic effects
- High risk patients
  - Old patient
  - Heart failure
  - Renal vascular disease
  - Surgery

NSAIDS's Side effects

- **Liver disease**
  - **Sulindac**
  - **Diclofenac**
  - **High dose of acetaminophen** (more than 4 gr)

- **CNS side effects:**
  - common with **Indomethacin**
    - **headache**
    - **vertigo**
    - **depression (in long term use)**
    - **psychosis (in long term use)**

NSAIDS's Side effects

In G6PD deficiency:

- Salicylates may cause haemolytic anaemia

In Pregnancy:

- Inhibit PG synthesis, thereby
- delay onset of labour and
- Increase chances of postpartum haemorrhage

In the newborn:

- Inhibition of PGs synthesis results in premature closure of the ductus arteriosus

NSAIDS's Drug-Interactions

- Unfortunately, NSAIDs can also potentiate, increase, or decrease the effect of many prescription drugs that this population takes.
- The most common interactions are with anticoagulants, oral hypoglycemics, diuretics, and antihypertensives.
- For example, use of ibuprofen with insulin or an oral hypoglycemic like may cause hypoglycemic effects because of the influence of prostaglandins on glucose metabolism

NSAIDS's Drug-Interactions

Examples for drug interactions

1. **Antihypertensives :** Na^+ retention by inhibition of renal PGs (vadodilators) formation
2. **Diuretics:** NSAIDs cause Na^+ retention & reduce diuretic efficacy
3. **Anticoagulants (warfarin) & antiplatelets:** increase risk of GIT bleeding **(relative)**

TABLE 17-5 Some Nonopioid Analgesics Approved for Acute Pain

Nonproprietary (Generic) Name	Proprietary (Trade) Name	Analgesic Dosage*	Maximum Daily Dose*
Aspirin (OTC)	ASA, others	650-1000 mg every 4-6 hours	4000 mg
Diflunisal	Dolobid	1000 mg to start, then 500 mg every 8-12 hours	1500 mg
Acetaminophen (OTC)	Tylenol, others	650-1000 mg every 4-6 hours	3000 mg
Ibuprofen (OTC)	Motrin, Advil, Nuprin, others	400-600 mg every 4-6 hours	3200 mg
Naproxen sodium (OTC)	Aleve	220-440 mg every 8 hours	660 mg
Fenoprofen	Nalfon	200 mg every 4-6 hours	1200 mg
Ketoprofen (OTC)	Orudis KT, Actron	12.5-25 mg every 4-6 hours	75 mg
Diclofenac	Cataflam	50 mg every 8 hours	150 mg
Etodolac	Lodine	200-400 mg every 6-8 hours	1200 mg
Ketorolac	Toradol	15-30 mg IV/IM to start, then 10-20 mg PO/IV/IM every 6 hours; no more than 5 days of therapy	60-120 mg