Nonsteroidal anti-inflammatory drugs

NSAIDs

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History of NSAIDs

- *Salix alba or White Willow bark*
- Sodium salicylate – 1875
- Acetylsalicylic acid – 1899
  - Also phenacetin and antipyrine
- Phenylbutazone – 1949
- Indomethacin - 1963

How often are NSAIDs used?

- >70 million prescriptions annually in the United States
- >30 billion doses used annually
- >60 years old patients, comprise over half of regular users.

Side Effects

- In 2001:
  - 100,000 hospitalizations (estimated)
  - 17,000 deaths (estimated)
  - $2 billion dollars in medical care

Main actions

1.) Analgesic

2.) Anti-inflammatory

3.) Anti-pyretic

4.) Anti-platelet

Others

5.) Useful in treatment of dysmenorrhoea

6.) Used to close the patent ductus arteriosus

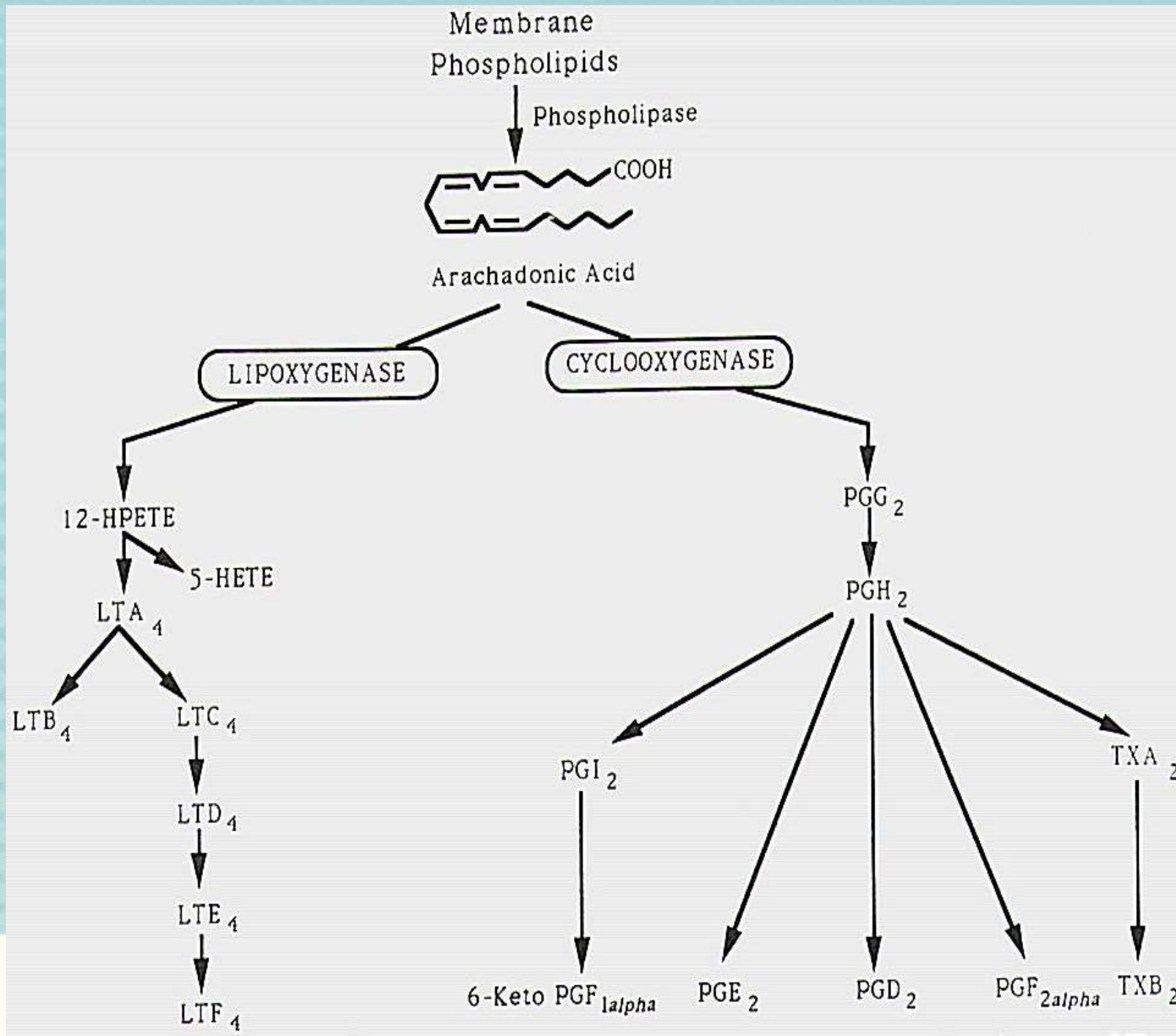
The classification of NSAIDs according to the chemical structure[8]

Salicylic acid derivates	Aspirin (acetylsalicylic acid) Sodium salicylate Salsalate Diflunisal Salsalate Sulfasalazine
Propionic acid derivates	Ibuprofen Naproxen Fenoprofen Flurbiprofen Ketoprofen Oxaprozin
Acetic acid derivatives	Diclofenac Etodolac Ketorolac Indomethacin Sulindac Tolmetin Nabumetone
Enolic acid derivatives	Pyrazolones: Phenylbutazone, Dipirone Oxicams: Piroxicam, Meloxicam, Tenoxicam, Lornoxicam
Fenamic acid derivatives (Fenamates)	Mefenamic acid Meclofenamic acid Flufenamic acid Tolfenamic acid
Selective COX-2 inhibitors (Coxibs)	Celecoxib Etoricoxib

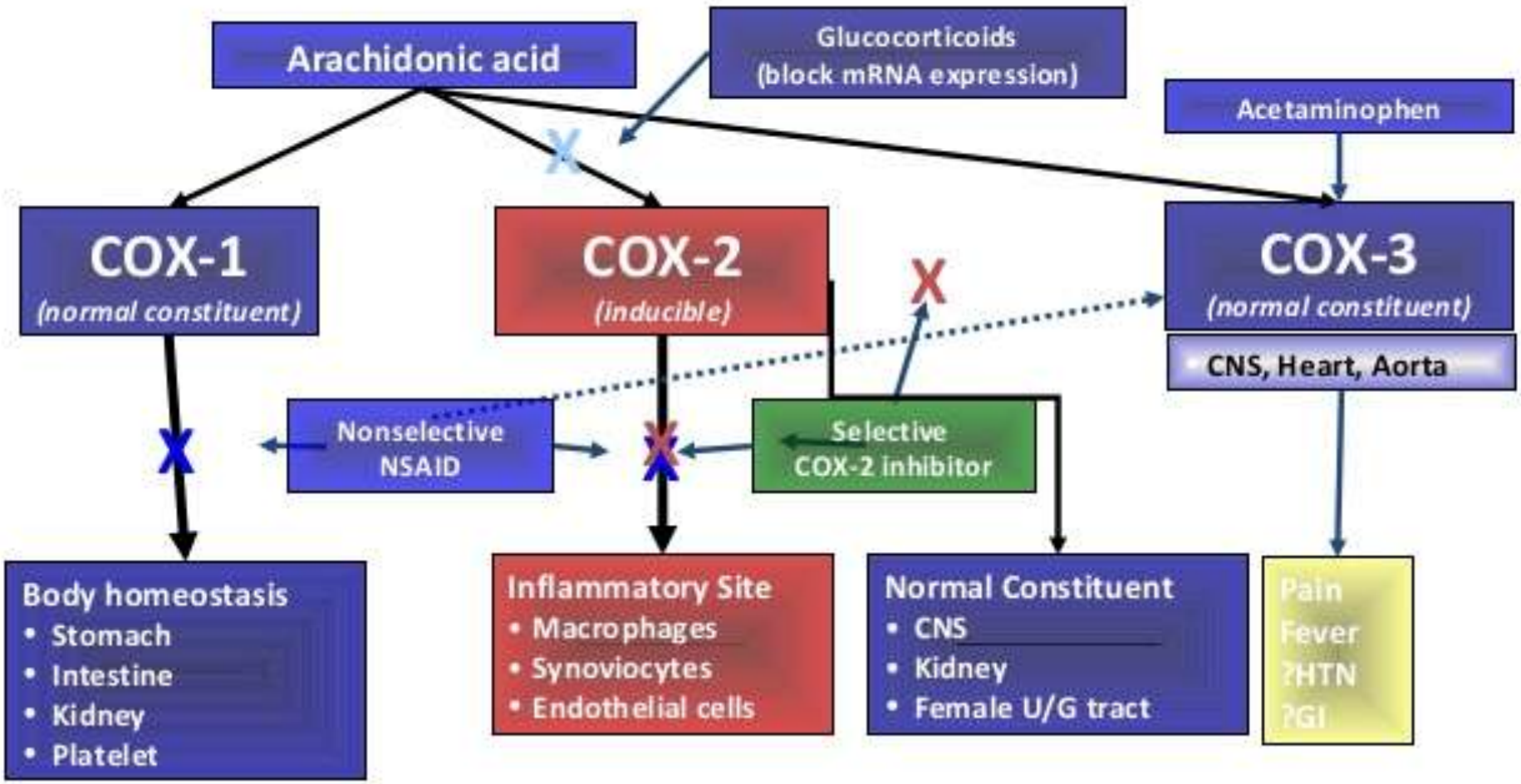
Familiar NSAIDs

- Acetylsalicylic acid
- Ibuprofen
- Naproxen
- Indomethacin
- Diclofenac
- Piroxicam
- Mefenamic acid
- Meloxicam
- Celecoxib

Eicosanoid Cascade



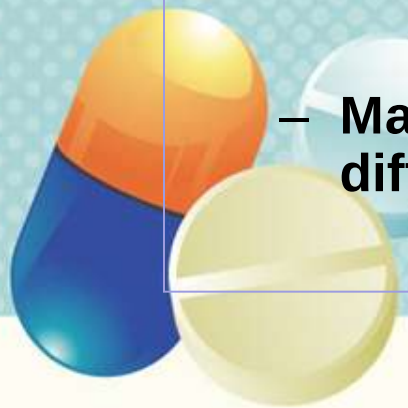
Proposed Mechanism: COX-1, COX-2, & COX-3



COX-1: Constitutive

Homeostatic

- **Protection of gastric mucosa**
- **Platelet activation**
- **Renal functions**
- **Macrophage differentiation**



COX-2: Regulated

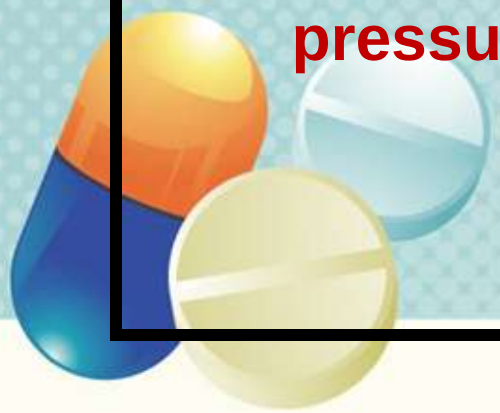
Pathologic

- Inflammation
- Pain
- Fever

Selective VER Non-Selective

- **Similar**
  - **Anti-inflammatory**
  - **Analgesic**
  - **Some renal effects, e.g. sodium excretion, blood pressure**

- **Different**
  - **No anti-platelet effects**
  - **Reduced endoscopic GI erosion and ulceration**
  - **No bronchial spasm**



Factors That Affect the Choice of Nonsteroidal Antiinflammatory Drugs

PROPERTIES OF THE DRUG	PATIENT CHARACTERISTICS
Efficacy	Individual variation
Tolerance	Disease being treated
Safety	Age
Convenience of dosage	Other diseases
Formulation	Other drugs
Cost	

NSAID Effects

- Analgesic dose = 50% - 75% anti-inflammatory dose
- Complete effects are achieved in two weeks in acute inflammatory conditions
- Inadequate response →NSAID of a different class

The "safest" NSAID

- NSAIDs with a short half-life and no enterohepatic circulation may be the best choices for older chronically ill patients

- Nonacetylated salicylates, ibuprofen

NSAIDs and surgery

- Four to five times the drug half-life
- NSAIDs should generally be discontinued at least three days before surgery
- Aspirin for at least one week prior to a planned surgical procedure to
- selective COX-2 inhibitors?

Topical NSAIDs

- Very safe
- Similar efficacy to oral NSAIDs for osteoarthritis for at least the first several weeks of treatment

ASA+NSAIDs

- Attenuation the effect of aspirin
- ↑ side effects of NSAIDs
- In patients on aspirin who require NSAIDs
  I. short-term basis
  II. aspirin should be taken at least two hours before the NSAID

Glucocorticoids+NSAIDs

- The risk of peptic ulcer disease increases significantly

PREGNANCY

- It is best to avoid NSAIDs
- Miscarriage
- Aspirin has a role in prevention of preeclampsia and the treatment of the antiphospholipid syndrome
- Closure of ductus arteriosus

LACTATION

- There is limited information
- NSAIDs are excreted in breast milk in very small amounts

NSAIDs in Older adults

- Pain complaints are common in the older population
- Most Older adults have comorbidities
- Elderly patients are at higher risk of NSAID-related adverse advents

NSAIDs + acetaminophen

- Avoid the combination of acetaminophen ≥2 g/day with an NSAID
- ↑ risk of gastrointestinal complications
- lack of clinically meaningful greater efficacy than with an NSAID alone

Enteric-coated tablets

- Enteric-coated Aspirin are supposed to have less GI symptoms than regular aspirin
- There is no evidence that the enteric coating decreases gastritis or peptic ulcers.

Slow release forms

- ↑ Side effects

Combination of two NSAIDs

- Combination therapy with more than one NSAID has no scientific rationale, and the risk for adverse effects is at least additive.

CARDIOVASCULAR EFFECTS

- ↑ Coronary risk
- Exacerbate heart failure
- Hypertension

Strategies to reduce cardiovascular risk

- Take low-dose ASA more than 2 hours before an NSAID.
- Do not use NSAIDs for 3 to 6 months after a cardiovascular event or procedure.
- Do not use extended-release preparations.
- Control blood pressure.

GASTROINTESTINAL

- Dyspepsia, peptic ulcer disease, and bleeding
- 103000 hospitalization and 16500 deaths
- 2% peptic ulcer

Risk factors for gastrointestinal adverse effects

- Age> 65 years
- Previous adverse reaction
- The use of anticoagulants, SSRIs and corticosteroids
- Liver disease
- CKD
- Smoking
- Excessive alcohol consumption
- Higher NSAID dose

How can decrease peptic ulcer?

- Use of alternative analgesics
- Lowest dose
- Selective COX2
- Misoprostol
- PPI
- Take medications after food

Kidney and NSAIDs

- Sodium retention
- Hypertension
- Acute renal failure
- Papillary necrosis
- Acute interstitial nephritis
- Accelerated chronic kidney disease

Kidney and NSAIDs

- All people with CKD should avoid NSAIDs
- NSAID nephrotoxicity can be exacerbated by ACE inhibitors or ARBs
- People with type 2 diabetes should avoid NSAIDs where possible.

PULMONARY EFFECTS

- Bronchospasm
- Pulmonary infiltrates

HEMATOLOGIC EFFECTS

- Cytopenias
- Antiplatelet effects

CENTRAL NERVOUS SYSTEM

- Aseptic meningitis
- Psychosis
- Cognitive dysfunction
- Headaches
- Tremor

SKIN REACTIONS

- Various skin reactions

- Toxic epidermal necrolysis (TEN) and the Stevens-Johnson syndrome

HEPATIC INJURY

- Elevations of serum aminotransferases
- Liver failure is quite rare
- Cholestasis

NSAIDs and IBD

- Non-selective NSAIDs and COX-2 inhibitors in people with ulcerative colitis and Crohn's disease may cause an exacerbation of symptoms

Drug–Drug Interactions Involving Nonsteroidal Antiinflammatory Drugs

DRUG AFFECTED	NSAID IMPLICATED	EFFECT
Warfarin	NSAIDs that inhibit COX-1	Inhibits metabolism of warfarin; increases risk of bleeding owing to inhibition of platelet function and gastric mucosal damage
Sulfonylurea	High-dose salicylate	Potentiates hypoglycemia
Beta-blocker	All PG-inhibiting NSAIDs	Blunts hypotensive but not negative chronotropic or inotropic effect
Hydralazine Prazosin ACE inhibitor	All PG-inhibiting NSAIDs	Loss of hypotensive effects
Diuretics	All PG-inhibiting NSAIDs	Loss of natriuretic, diuretic, hypotensive effects of furosemide Loss of natriuretic effect of spironolactone Loss of hypotensive but not natriuretic or diuretic effects of thiazide
Phenytoin	Other NSAIDs	Displaces phenytoin from plasma protein, reducing total concentration for the same active concentration
Lithium	Most NSAIDs	Increases plasma lithium level
Digoxin	Most NSAIDs	May increase digoxin levels
Aminoglycosides	Most NSAIDs	May increase aminoglycoside level
Methotrexate	Most NSAIDs	May increase methotrexate plasma concentration
Sodium valproate	Aspirin	Inhibits valproate metabolism, increasing plasma valproate concentration

Warfarin+NSAID

- ↑ serum levels of warfarin
- serious bleeding

Lithium+ NSAIDs

- ↑ lithium
- serious adverse effects: confusion, tremor, slurred speech, and vomiting.

Laboratory monitoring

- Age
- Dose
- Comorbidities
- Other medications

To maximize patient safety

- Acetaminophen is safer than NSAIDs for most conditions
- Patient evaluation for risk of developing NSAID-induced toxicity
- Prescribe all NSAIDs with caution, in all patient groups
- Lowest effective NSAID dose
- The shortest possible time

To maximize patient safety

- Patients should be advised about adverse effects
- Patients should be regularly monitored when taking NSAIDs
- Consider adding codeine to paracetamol in select patients


Thank You!