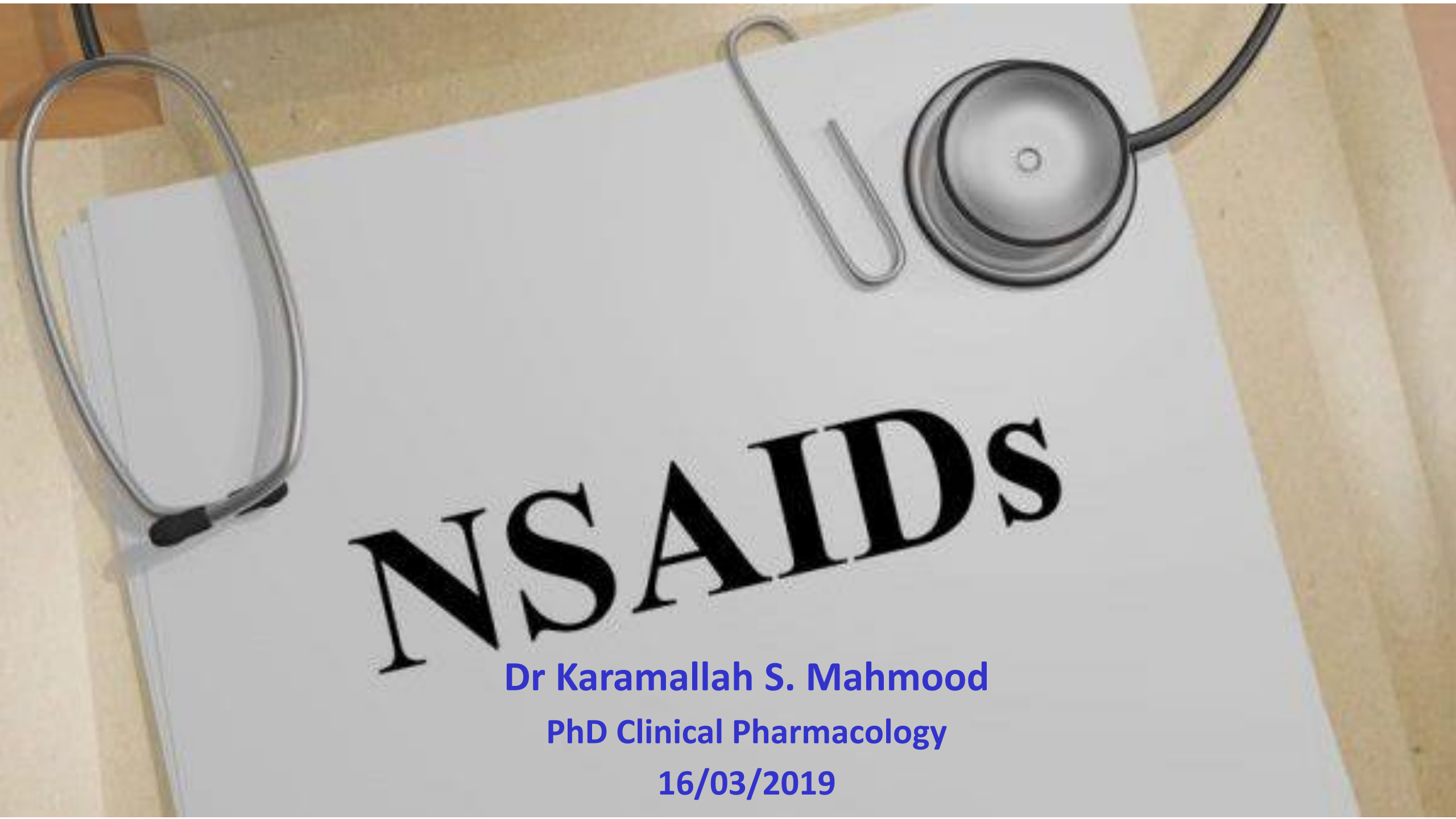


Dr Karamallah S. Mahmood

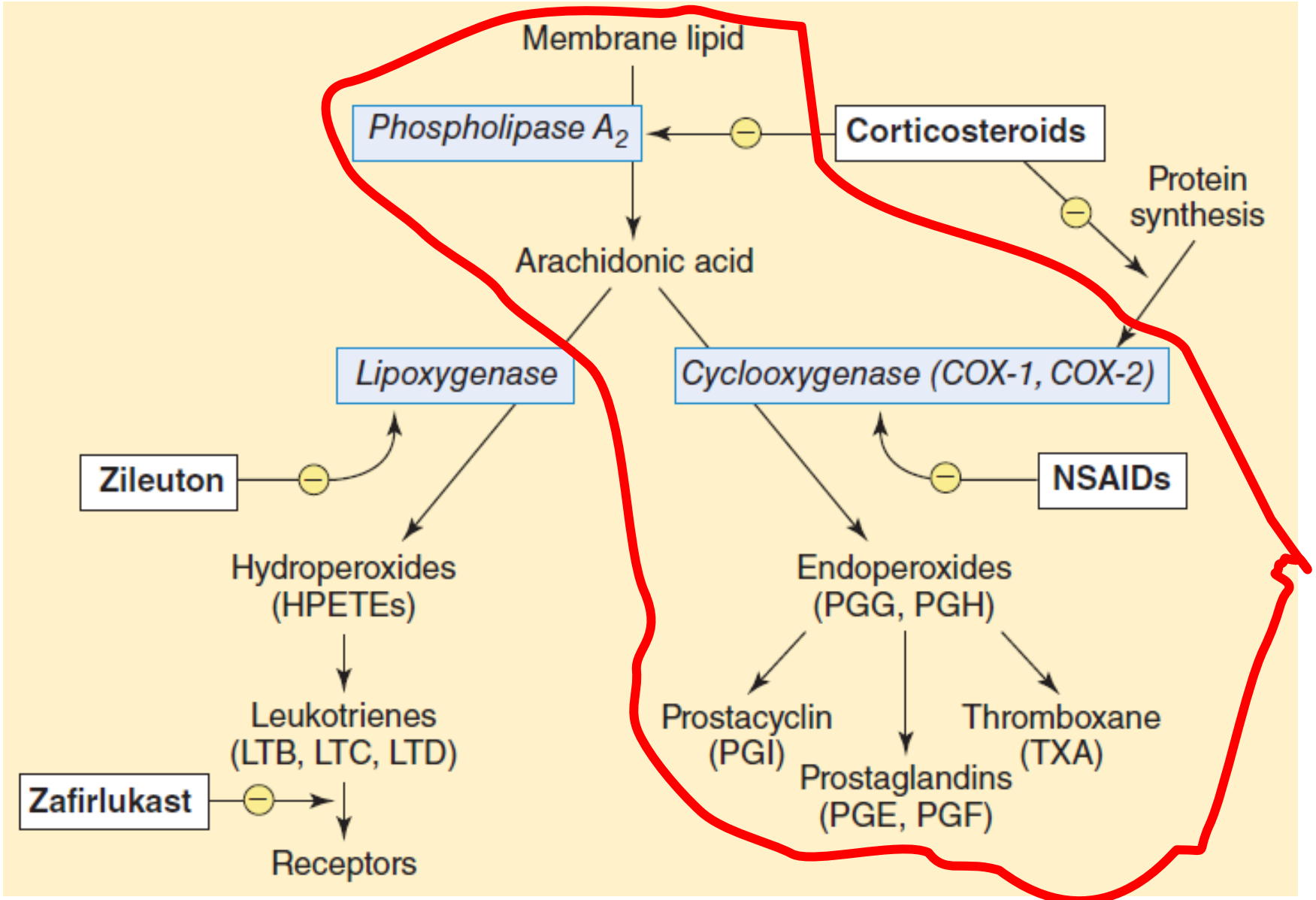
PhD Clinical Pharmacology

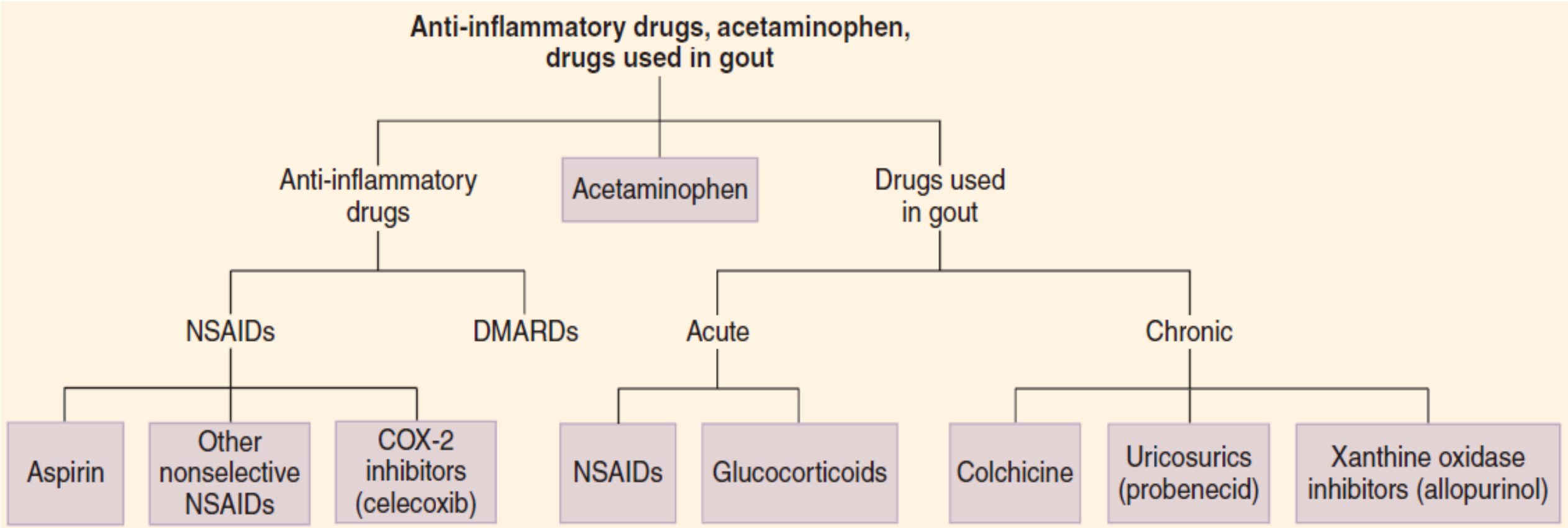
16/03/2019

Autacoids

- **Amines:**
  - Histamine
  - 5-Hydroxytryptamine
- **Peptide:**
  - Bradykinin
  - Angiotensin
- **Lipids:**
  - Leukotriens
  - Prostaglandins

Lipids/ Eicosanoid




Anti-inflammatory drugs, acetaminophen, drugs used in gout
Anti-inflammatory drugs
Acetaminophen
Drugs used in gout
NSAIDs
DMARDs
Acute
Chronic
Aspirin
Other nonselective NSAIDs
COX-2 inhibitors (celecoxib)
NSAIDs
Glucocorticoids
Colchicine
Uricosurics (probenecid)
Xanthine oxidase inhibitors (allopurinol)

Anti-inflammatory, Antipyretic, and Analgesic Agents

I. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

A. Aspirin and other NSAIDs
B. Celecoxib

II. ACETAMINOPHEN

Drug	Half-life (hours)
Aspirin	0.25
Celecoxib	11
Diclofenac	1.1
Diflunisal	13
Etodolac	6.5
Fenoprofen	2.5
Flurbiprofen	3.8
Ibuprofen	2
Indomethacin	4–5
Ketoprofen	1.8
Ketorolac	4–10
Meloxicam	20
Nabumetone[a]	26
Naproxen	14
Oxaprozin	58
Piroxicam	57
Sulindac	8
Tolmetin	1

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The NSAIDs are a group of **chemically dissimilar** agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of:

Salicylic acid (*aspirin, diflunisal , salsalate*)

Propionic acid (*ibuprofen, fenoprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin*)

Acetic acid (*diclofenac, etodolac, indomethacin, ketorolac, nabumetone, sulindac, tolmetin*)

Enolic acid (*meloxicam, piroxicam*)

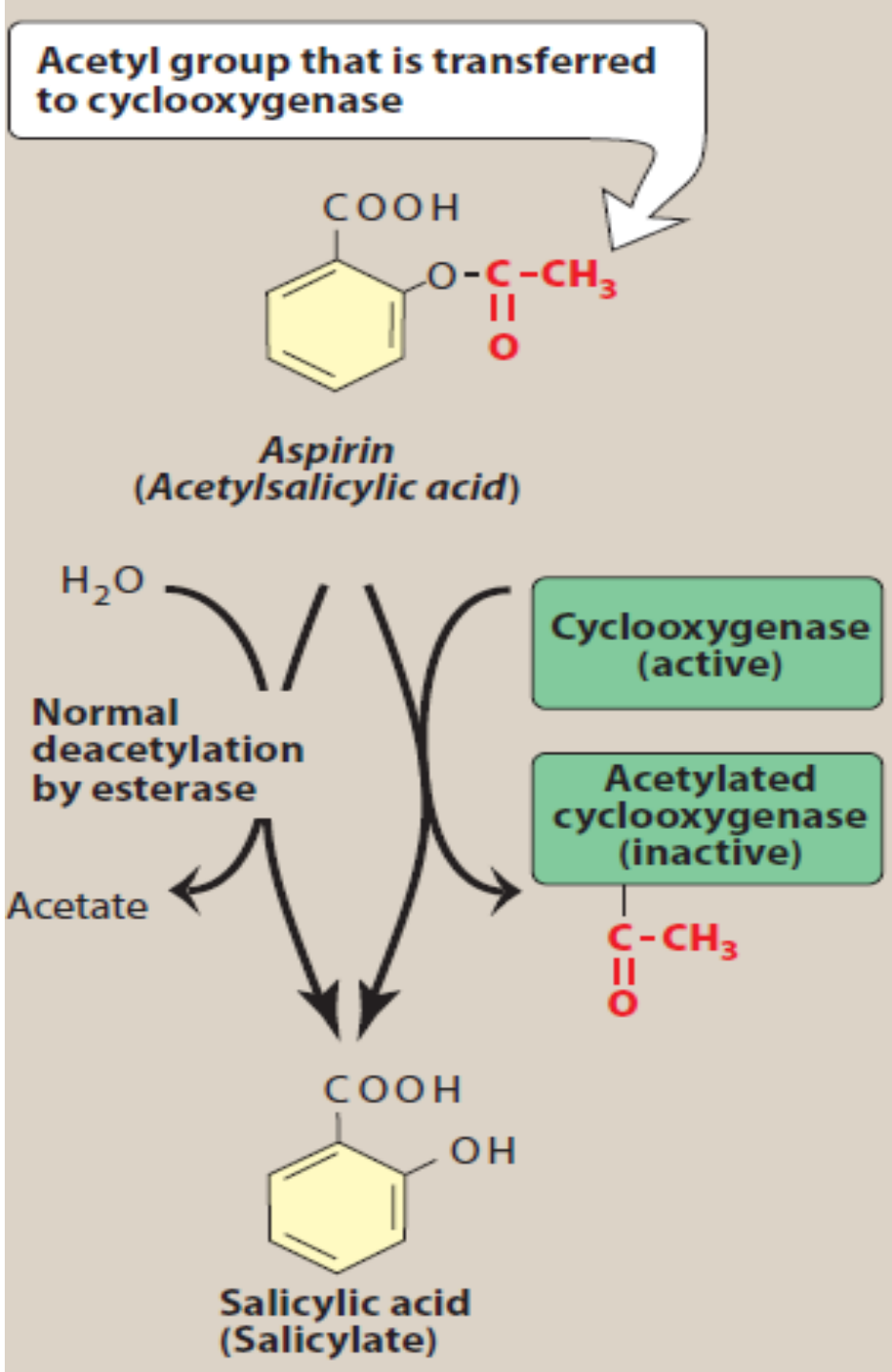
Fenamates (*mefenamic acid, meclofenamate*)

Selective COX-2 inhibitor (*celecoxib*)

NSAIDs

MOA:

NSAIDs are weak organic acid that **acetylates**/ inactivates COX



NSAIDs/ Pharmacological Effects:

a. Anti-inflammatory actions:

COX inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation

b. Analgesic action:

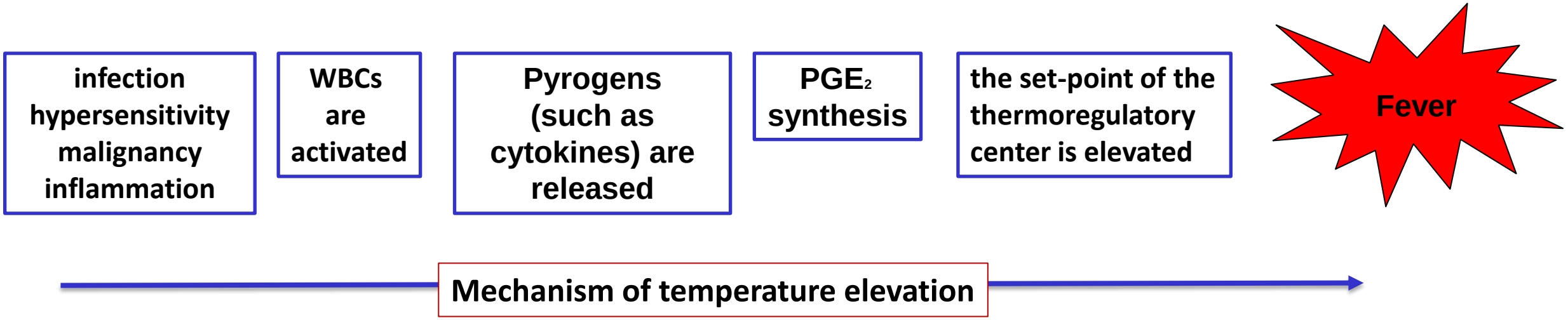
PGE2 **sensitizes** nerve endings to the action of bradykinin, histamine, and other mediators
Thus, by decreasing PGE2 synthesis, the sensation of pain can be decreased.
All agents are generally considered to have equivalent efficacy.

- Used mainly for the management of mild to moderate pain arising from musculoskeletal disorders.

Ketorolac can be used for more severe pain but for only a short duration.

NSAIDs/ Pharmacological Effects:

c. Antipyretic action:



- NSAIDs have no effect on normal body temperature, **WHY??**

NSAIDs/ Therapeutic Uses

a. Anti-inflammatory and analgesic uses:

NSAIDs are used in the treatment of:

- Osteoarthritis, gout, and RA
- Common conditions (e.g headache, arthralgia, myalgia, and dysmenorrhea)

Opioids + NSAIDs → **Malignancy**

Opioids + NSAIDs → **Opioid-sparing effect/ lower doses of opioids**

Salicylates:

Low doses → **Antiplatelet**

High doses → **analgesic**

Higher doses → **analgesic + anti-inflammatory**

NSAIDs/ Therapeutic Uses

b. Antipyretic uses:

Aspirin, ibuprofen, and naproxen

Aspirin should be avoided in patients less than 20 years old with viral infections, to prevent Reye syndrome

Reye's syndrome is a rare but serious condition that results in microvesicular hepatitic steatosis (fatty changes of the liver) and acute encephalopathy (altered mental status) primarily in children and teenagers recovering from a viral illness (such as influenza or varicella zoster virus).

The underlying problem with the use of aspirin during a viral illness is **an inhibition of fatty acid metabolism** in the liver

NSAIDs/ Therapeutic Uses

c. Cardiovascular applications:

Aspirin: (**low doses**)
Inhibits COX-1–mediated production of **TXA2**
Used to inhibit platelet aggregation and vasoconstriction

Aspirin are used **prophylactically** to reduce the risk of recurrent cardiovascular events and/or death in patients:

1) with previous MI, unstable angina pectoris, TIA or stroke,
3) in high-risk patients such as those with chronic stable angina or diabetes

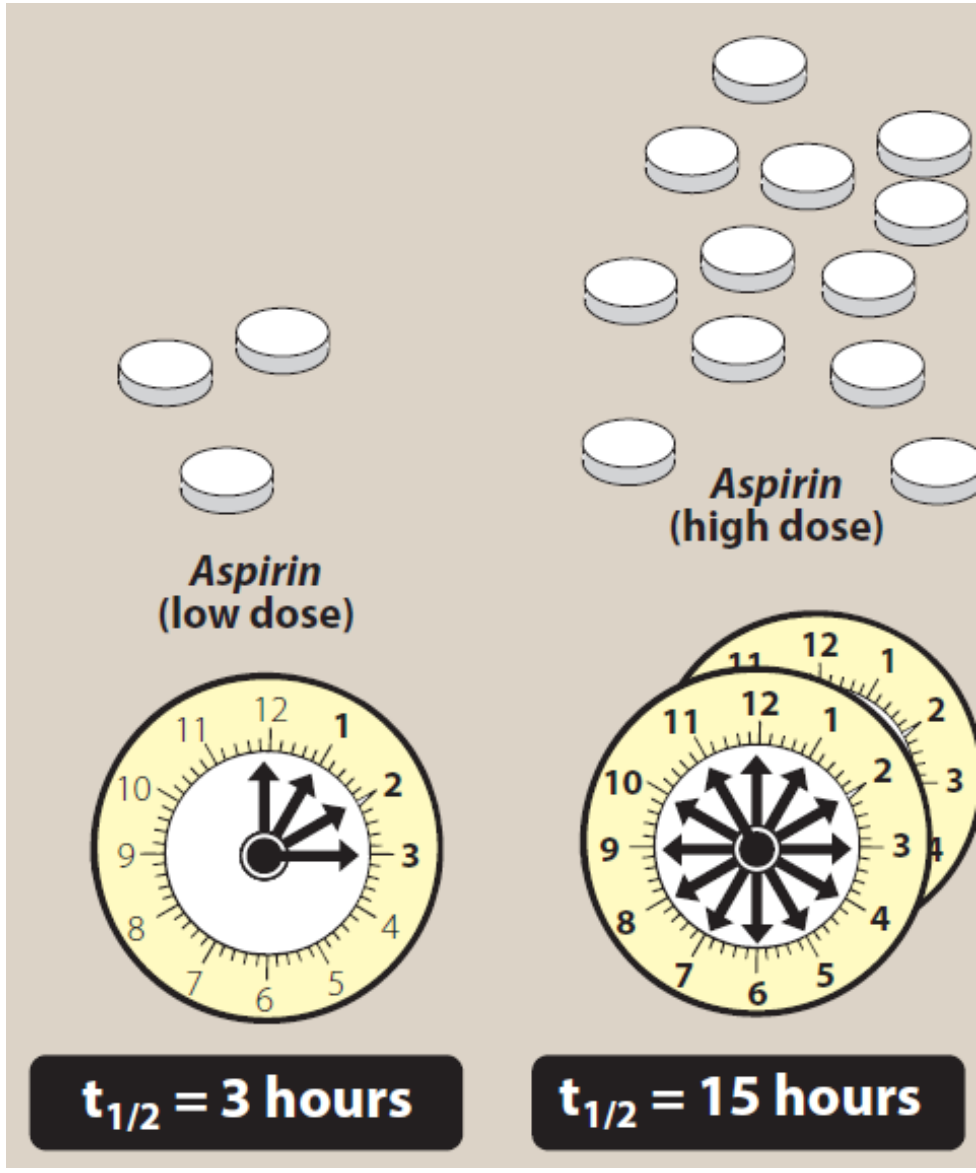
NSAIDs/ Pharmacokinetics:

Aspirin:

- **oral** administration
- cross the BBB, placenta and are absorbed through intact skin
- cleared by the **kidney**, resulting in **first-order elimination** (t1/2 3.5 hours)

- At anti-inflammatory dosages (**more than 4 g/day**), the **hepatic** metabolic pathway becomes saturated (**zero-order kinetics**) and t1/2 of 15 hours

- **At low doses of aspirin (less than 2 g/day), uric acid secretion is decreased**
- **At high doses, uric acid secretion may be unchanged or increased**



NSAIDs/ Pharmacokinetics:

Other NSAIDs:

- Well absorbed after oral administration
- Highly bound to plasma proteins
- Metabolized by the liver to inactivate metabolites
- Few (nabumetone and sulindac) have active metabolites
- Elimination primarily via the urine.

NSAIDs/ Adverse events

a. Gastrointestinal: (most common)

- Ranging from dyspepsia to bleeding
- By inhibiting of **PGE2 and PGF2α**
- Agents with a higher selectivity for COX-1 may have a higher risk for GI events

b. Increased risk of bleeding (antiplatelet effect):

COX-1–mediated **TXA2** formation (TXA2 enhances platelet aggregation)

Because platelets lack nuclei, they cannot synthesize new enzyme when inhibited by aspirin, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days).

NSAIDs/ Adverse events

c. Actions on the kidney:

- **PGE2 and PGI2** are responsible for maintaining renal blood flow
- NSAIDs can result in retention of sodium and water

d. Cardiac effects:

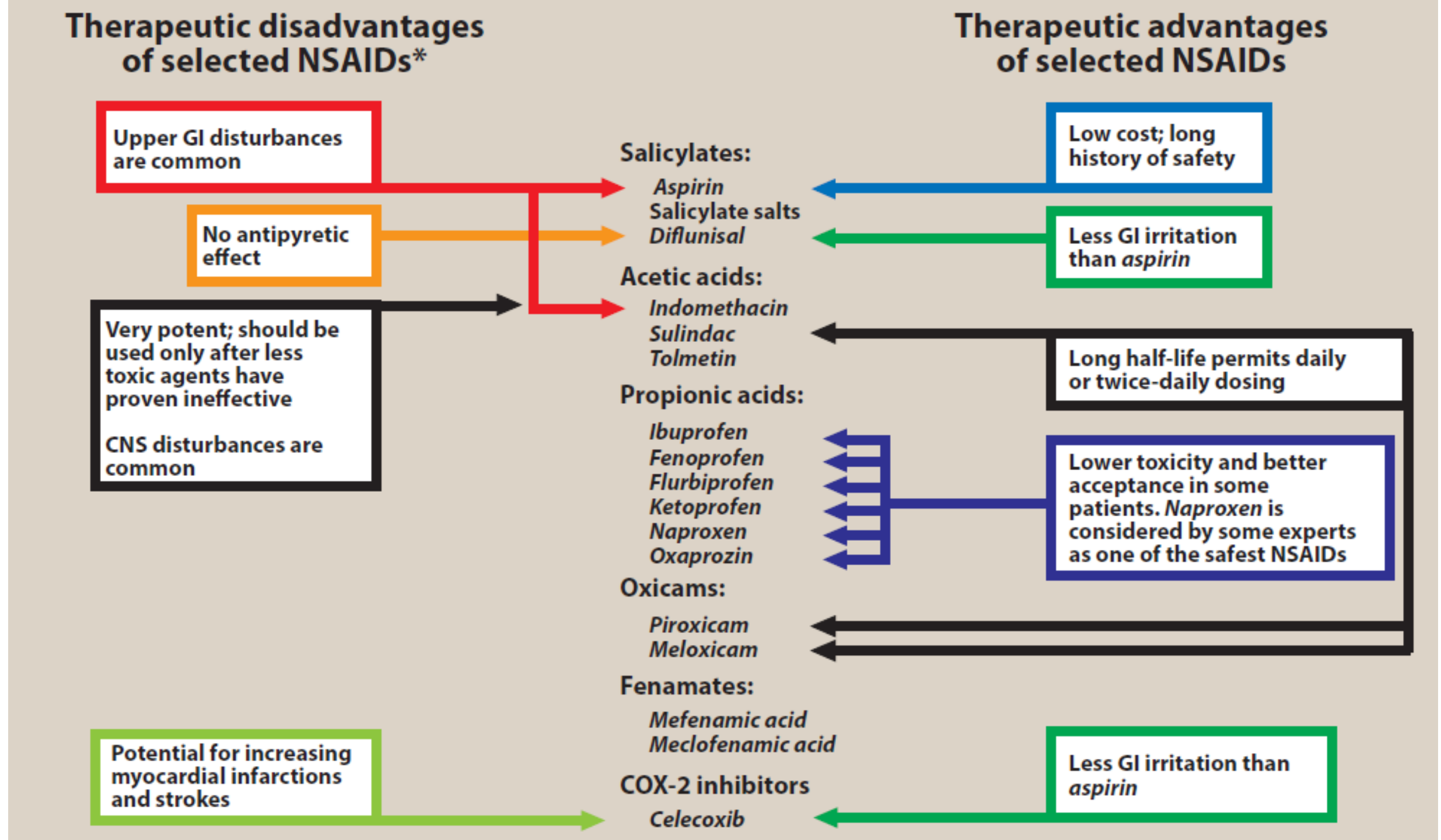
Agents with higher relative **COX-2 selectivity** have been associated with an increased risk for cardiovascular events, possibly by decreasing **PGI2** production mediated by COX-2.

- **NSAIDs should be used with caution in patients with asthma, why??**

Pregnancy: (Acetaminophen is preferred) NSAIDs should generally be avoided

Celecoxib

- Selective **COX-2 inhibitor**
- Treatment of RA, osteoarthritis, and acute mild to moderate pain
- Associated with **less GI bleeding** and dyspepsia than other NSAIDs


Therapeutic disadvantages of selected NSAIDs*
Therapeutic advantages of selected NSAIDs
Upper GI disturbances are common
No antipyretic effect
Very potent; should be used only after less toxic agents have proven ineffective
CNS disturbances are common
Potential for increasing myocardial infarctions and strokes
Salicylates:
Aspirin
Salicylate salts
Diflunisal
Acetic acids:
Indomethacin
Sulindac
Tolmetin
Propionic acids:
Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin
Oxicams:
Piroxicam
Meloxicam
Fenamates:
Mefenamic acid
Meclofenamic acid
COX-2 inhibitors
Celecoxib
Low cost; long history of safety
Less GI irritation than aspirin
Long half-life permits daily or twice-daily dosing
Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs
Less GI irritation than aspirin

ACETAMINOPHEN

- Inhibits prostaglandin synthesis in the **CNS**.

- **Indicated as analgesic and antipyretic for:**
  - ✓ **Patients with gastric complaints/ risks**
  - ✓ **Children with viral infections or chickenpox, WHY??**

At normal therapeutic doses, acetaminophen is virtually free of significant adverse effects

large doses: Hepatic necrosis, a very serious and potentially life threatening condition