



Farmakologi ANALGETIK, ANTIINFLAMASI dan ANTIPIRETIK

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DEFINISI NYERI

= Pengalaman sensorik dan emosional yang tidak menyenangkan akibat **kerusakan jaringan**, baik aktual maupun potensial, atau yang digambarkan dalam bentuk kerusakan tersebut



MEKANISME PROTEKSI TUBUH

(berfungsi melindungi & memberi tanda bahaya)

JENIS NYERI

Menurut Sumber Nyeri :

■ NYERI NOSISEPTIF / NYERI INFLAMASI

- adanya kerusakan / inflamasi jaringan → ujung saraf menerima rangsang nyeri

■ NYERI NEUROPATIK

- berhub dg lesi sist syaraf perifer / sentral
- mis. Neuropatik DM, kompresi serabut saraf, neuroma

■ NYERI NOSISEPTIF-NEUROPATIK

Menurut lamanya,

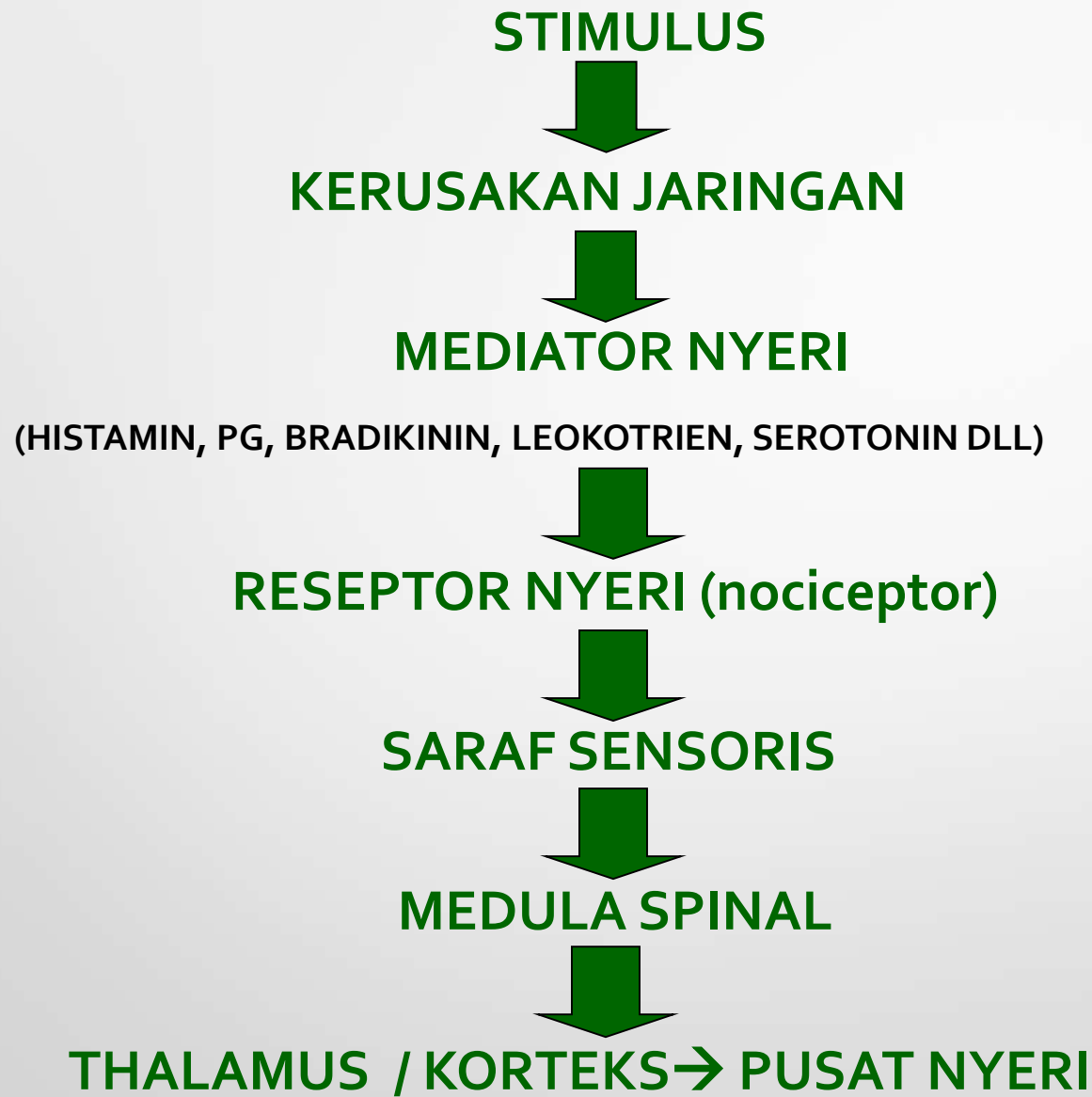
😊 AKUT

- terjadi segera setelah trauma, operasi, atau lesi saraf

😊 KRONIK

- terjadi kontinu (minimal 3 bulan)

PROSES TIMBULNYA NYERI



Transduksi

Transmisi

Modulasi

Persepsi

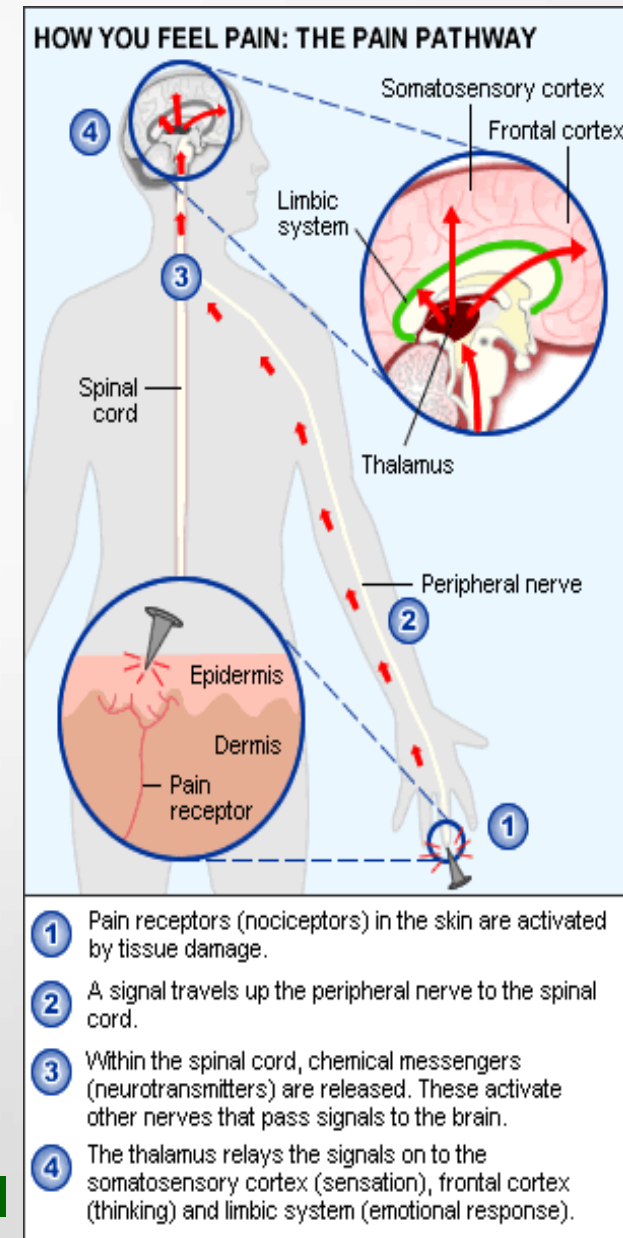


Table 3-3. Mediators of acute inflammation.

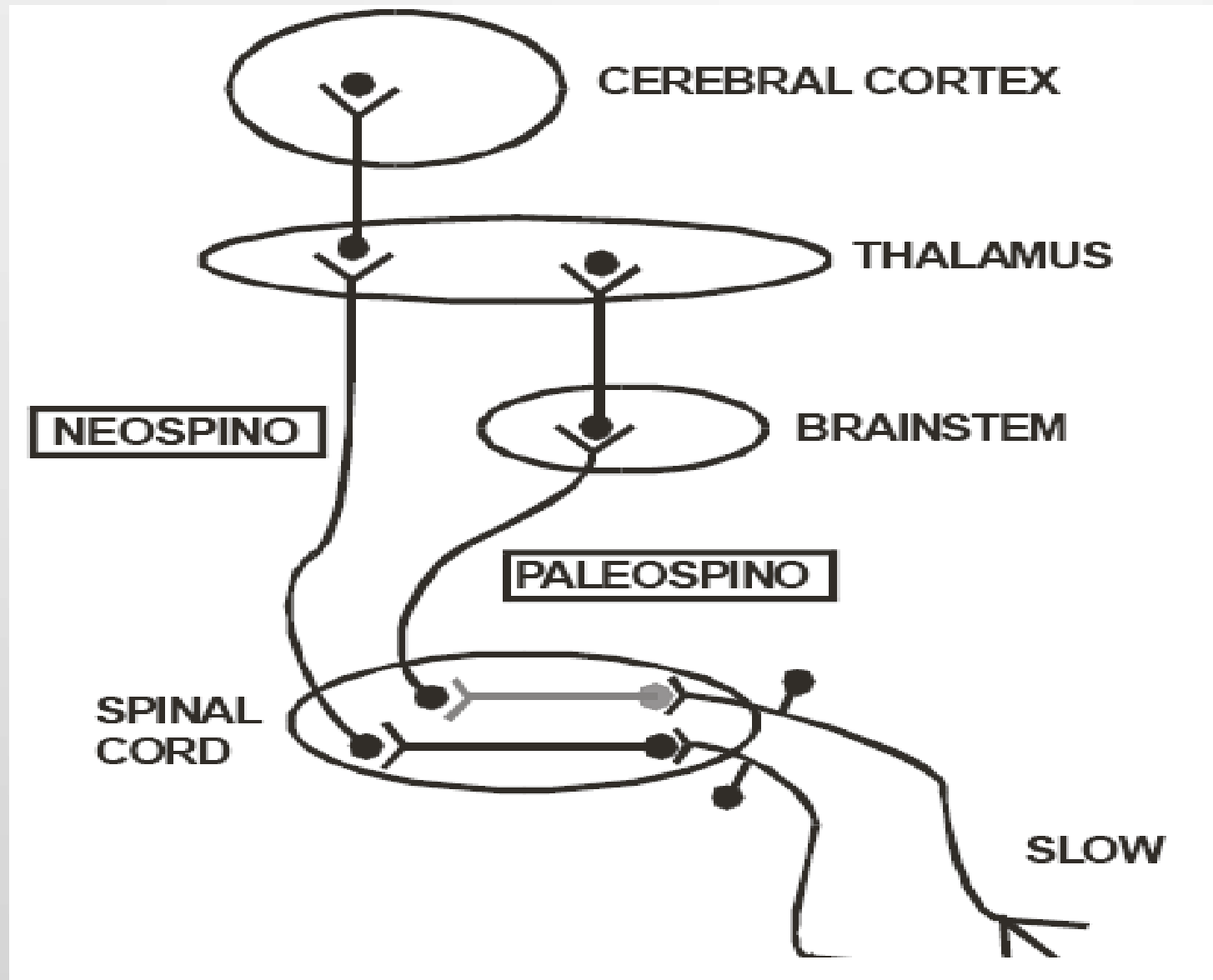
Mediator	Vasodilation	Increased Permeability		Hemostasis	Opsonin	Pain
		Immediate	Sustained			
Histamine	+	+++	-	-	-	-
Serotonin (5-HT)	+	+	-	-	-	-
Bradykinin	+	+	-	-	-	+++
Complement 3a	-	+	-	-	-	-
Complement 3b	-	-	-	-	+++	-
Complement 5a	-	++	-	+++	-	-
Prostaglandins	+++	+	+?	+++	-	+
Leukotrienes	-	+++	+?	+++	-	-
Lysosomal proteases	-	-	++ ¹	-	-	-
Oxygen radicals	-	-	++ ¹	-	-	-

¹Proteases and oxygen-based free radicals derived from neutrophils are believed to mediate a sustained increase in permeability by means of their damage to endothelial cells.

JALUR TRANSMISI NYERI

	FAST	SLOW
Stimulated by:	Mechanical Thermal	Chemical (K ⁺ , bradykinin)
Pain Sensation	Sharp Acute	Aching, nauseous Chronic
Fiber Type to Spinal Cord	A _δ (small 1–5 μm, myelinated)	C (small 0.5–2 μm, unmyelinated)
Transmission Velocity	6 - 30 m/sec	0.5 - 2 m/sec
Purpose of Sensation	Remove pain rapidly	Seek medical attention

FAST & SLOW PAIN PATHWAY



Each pathway terminates in a different CNS area

Fast Pain Pathway: Most all fibers pass to thalamus and terminate in the “*ventrobasal complex*”. Signals then further ascend to somatosensory cortex – i.e. localization of pain source is good.

Slow Pain Pathway: Terminates widely in brainstem with _ of fibers continuing on to the thalamus. i.e. terminates in lower brain regions when compared with fast pathway and localization of pain source is poor.

The principal neurotransmitter for each pathway is different

Fast Pain Pathway: Glutamate, a common short acting CNS excitatory neurotransmitter.

Slow Pain Pathway: Mainly substance P, slow release taking seconds or minutes to reach maximal concentration.

INFLAMASI / RADANG

Stimuli : panas, bhn kimia, mekanik

Tujuan tubuh menimbulkan reaksi radang :

1. Menetralkan dan menghancurkan bahan berbahaya
2. Mencegah penyebaran bahan berbahaya
3. Memperbaiki kondisi yang rusak

Proses yang terjadi :

- ✓ kerusakan mikrovaskular
- ✓ peningkt permeabilitas kapiler
- ✓ migrasi lekosit ke jar radang.

Mediator kimiawi yang dilepas secara lokal

histamin, 5 HT, bradikinin, PAF, substance P, tromboksan, proton, radikal bebas, leukotrien, prostaglandin

**Tanda radang →
cardinal signs :**

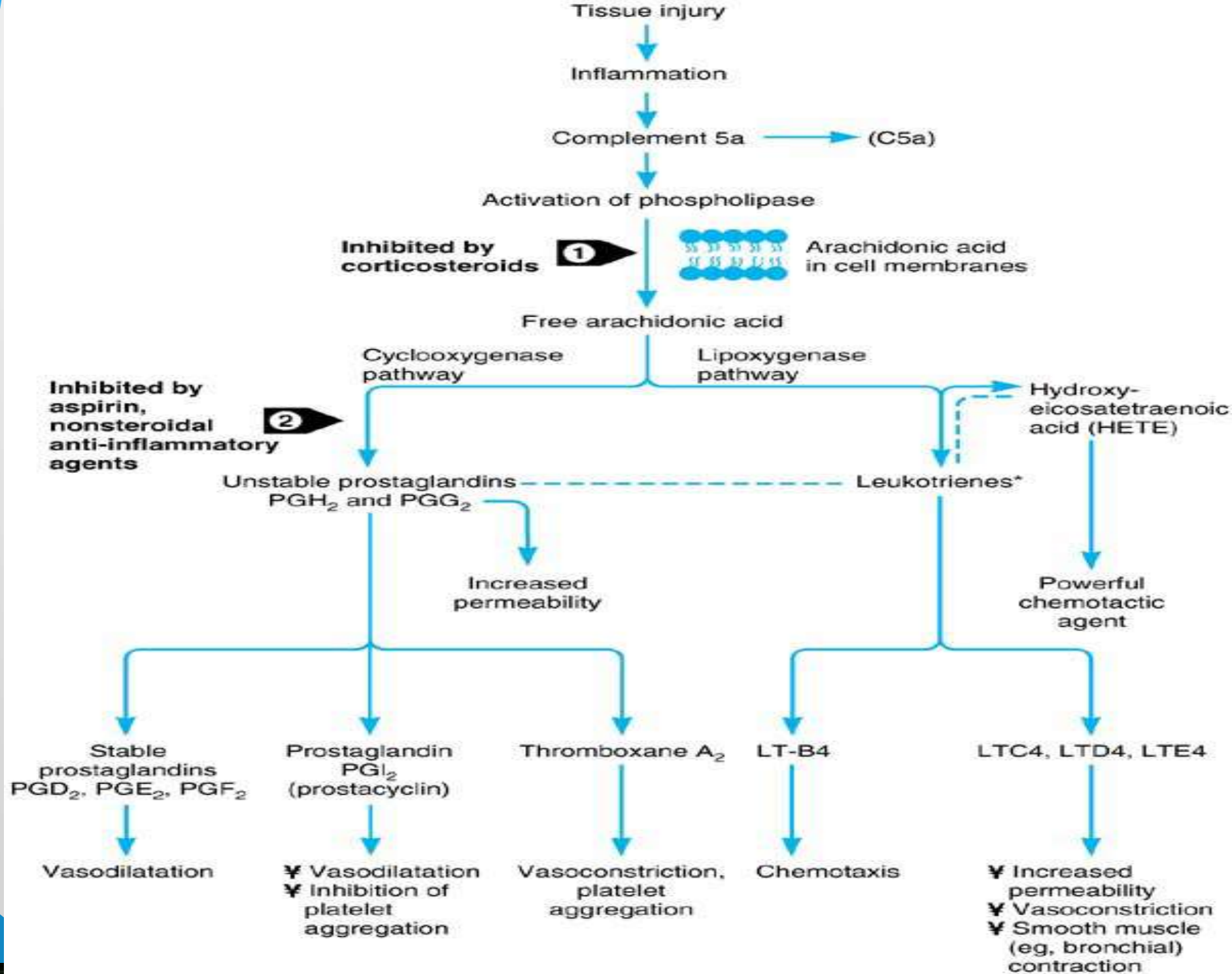
😊 rubor

😊 calor

😊 tumor,

😊 **dolor**

😊 functiolaesa



PENATALAKSANAAN NYERI

Tx Non-Farmakologis

**Tx Farmakologis/
Ox antinyeri**

Non-Opioid

Opioid

NSAID

**Paracetamol,
Tramadol, dll**

**Morfin,
Pethidin, dll**

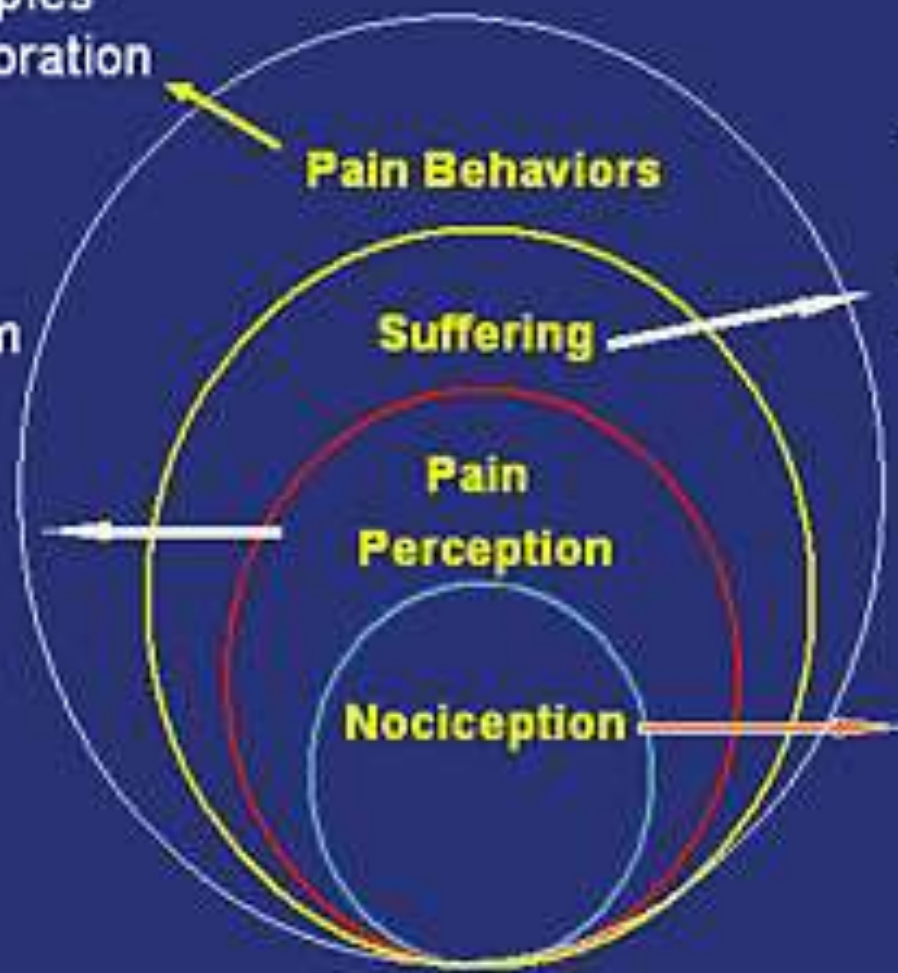
**Specific
COX2-inh**

**Non specific
/Konvensional**

Pain: A Conceptual Approach to Treatment

- Cognitive therapies
- Functional restoration

- Opioids/Ultam
- Adjuvants
- ?NSAIDS
- ?Tylenol
- Neural-augmentation
- Ablative surgery



- Antidepressants/psychotropics
- Relaxation
- Spiritual

- Local blocks
- NSAIDS
- Surgery
- Physical modalities

TERAPI NYERI : NON-FARMAKOLOGIK

Cognitive-Behavioral

- Relaxation
- Preparatory information
- Hypnosis

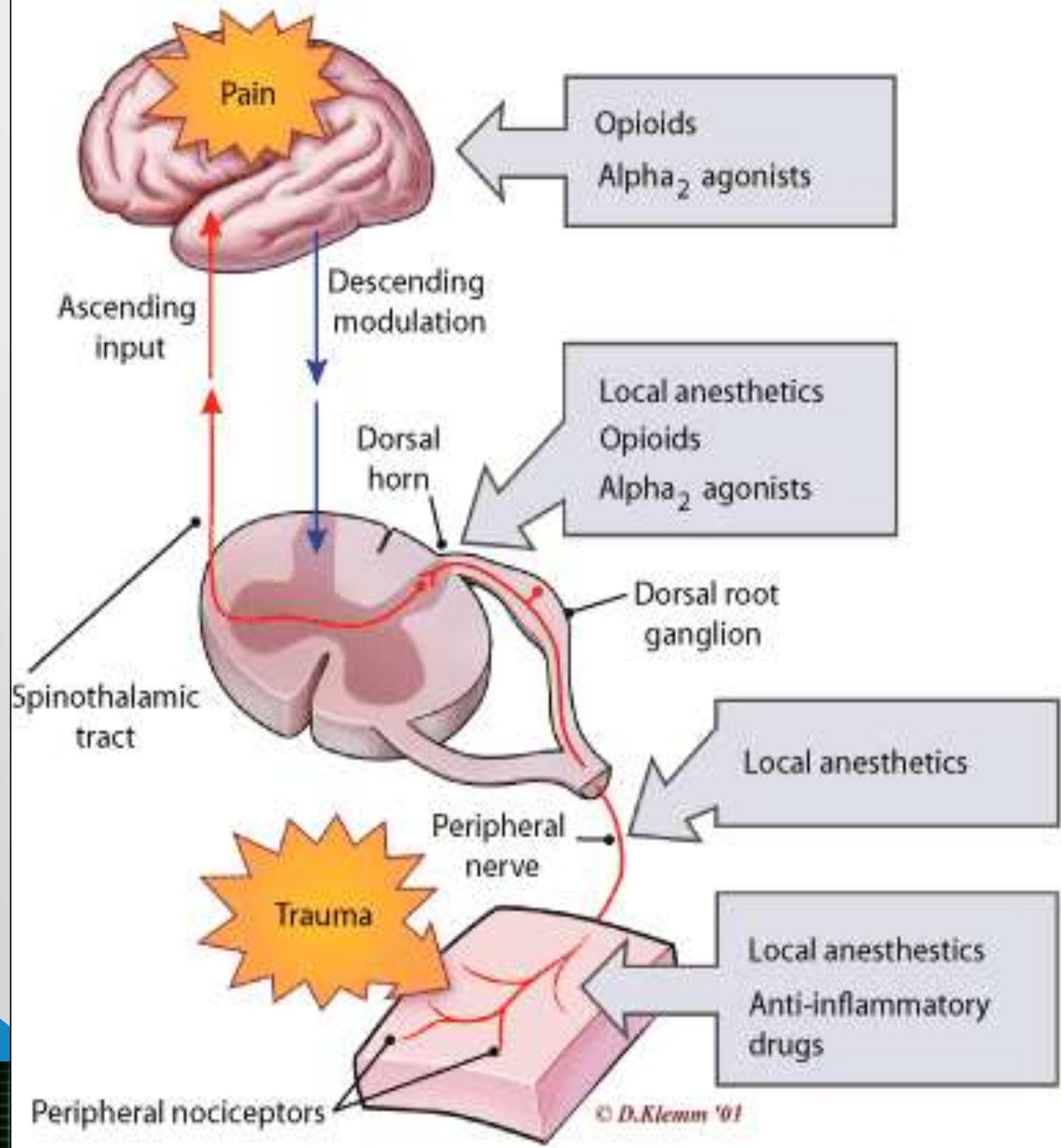
Physical Agents

- Application of superficial heat and cold
- Massage
- Exercise
- Immobilization
- Electroanalgesia (eg, TENS= *transcutaneous electrical nerve stimulation*)
- Acupuncture

TERAPI FARMAKOLOGIS

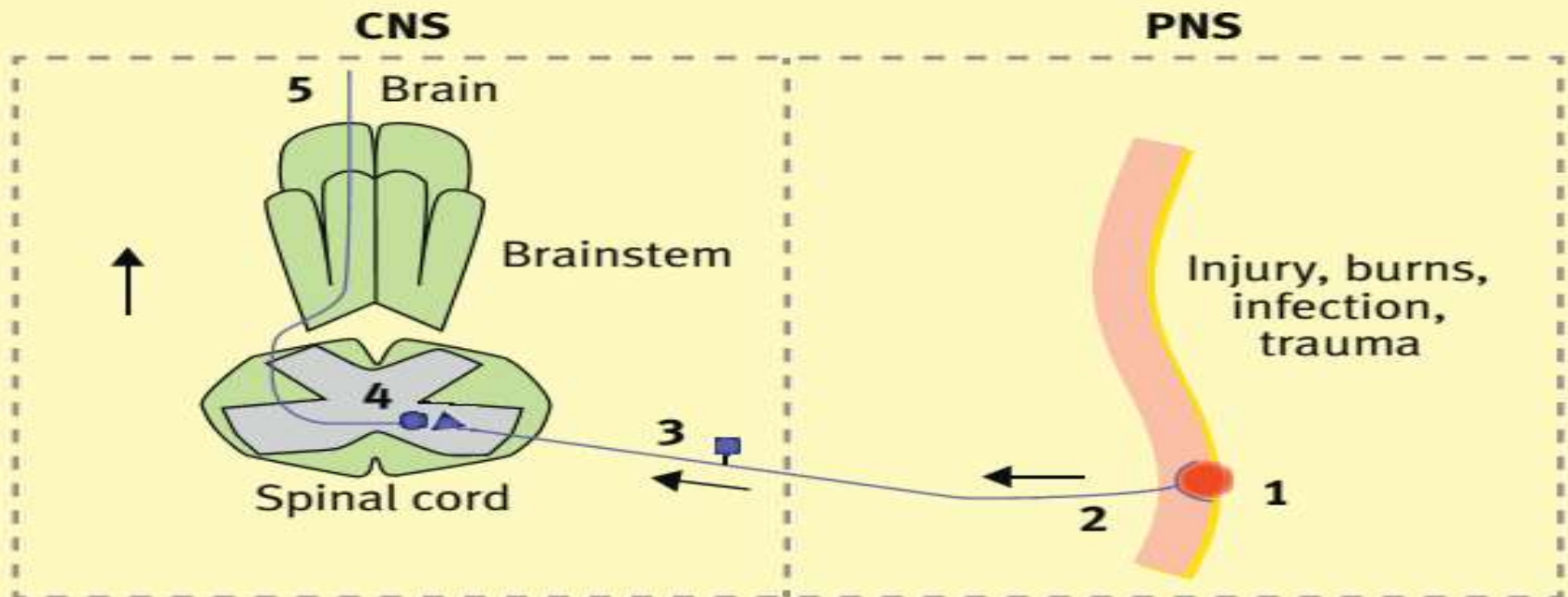
Bds target kerja obat :

1. Menghambat mediator nyeri (transduksi):
 - Analgetik non-opioid (NSAID, dll)
 - Antiinflamasi steroid
2. Menghambat transmisi nyeri
 - anestesi lokal
3. Blokade pusat nyeri di SSP (Persepsi)
 - Analgesik opioid
 - Paracetamol
 - Anestesi umum



Tx FARMAKOLOGIS

The common pathway of nociception



Opioids
Calcium channel antagonists
NMDA antagonists
Paracetamol
Adrenoceptor agonists
Gabapentin/pregabalin

LOX inhibitors
COX inhibitors
Local anaesthetics
TRPV1 agonists/antagonists

Classes of non-opioid drugs and their mechanisms

Mechanism

Inhibition of the release of local mediators

Prototypical example

Anti-inflammatory drugs
(e.g. *Non-steroidal anti-inflammatory drugs, paracetamol*)

Peripheral modulation

TRPV1

Spinal modulation

TENS^a
GABA^b
NMDA^c

Modulation of central transmission

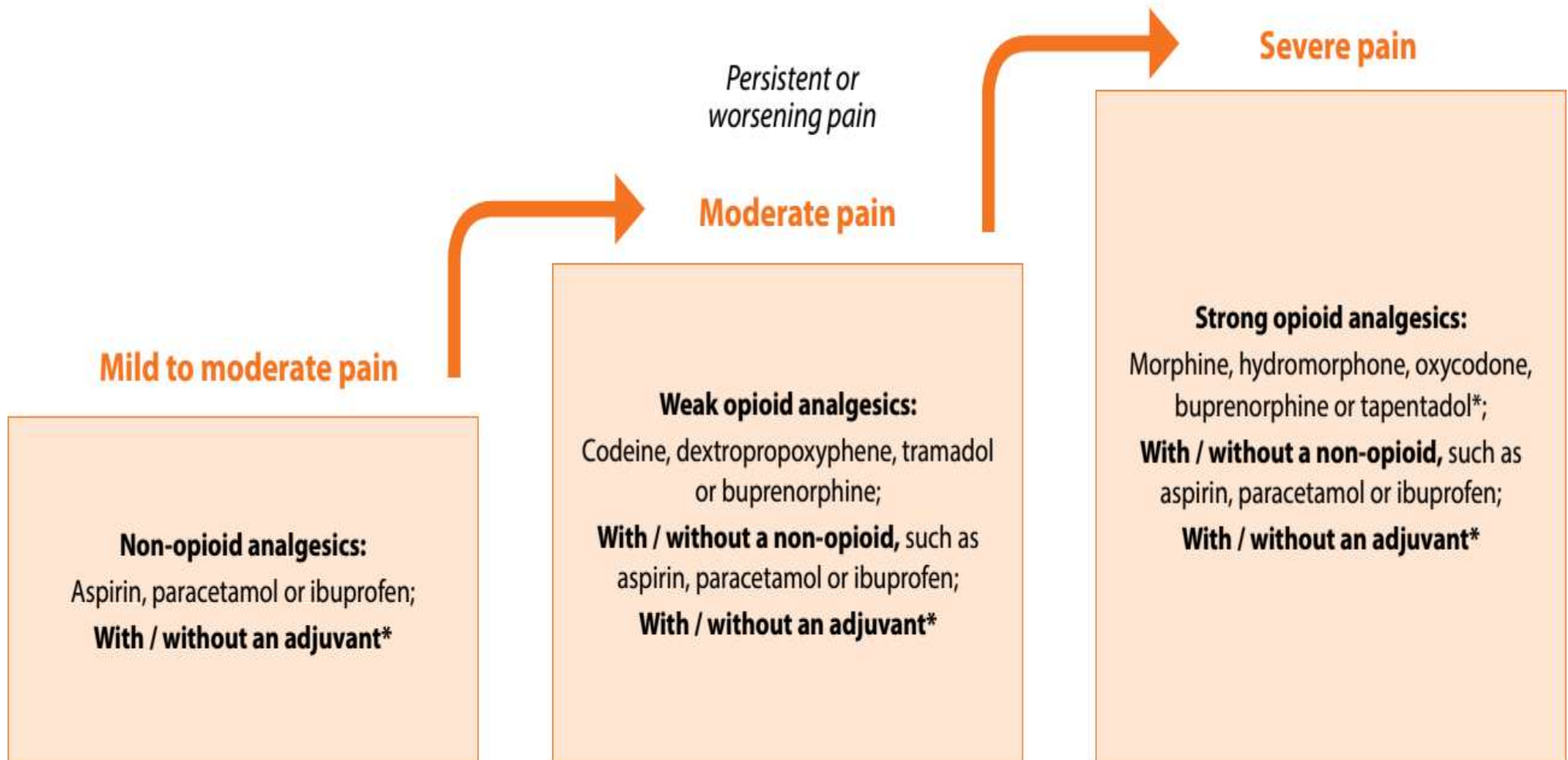
Cannabinoid ligands
Behavioural therapies

^a Transcutaneous Electrical Nerve Stimulation.

^b γ -Aminobutyric acid.

^c *N*-Methyl D-aspartate.

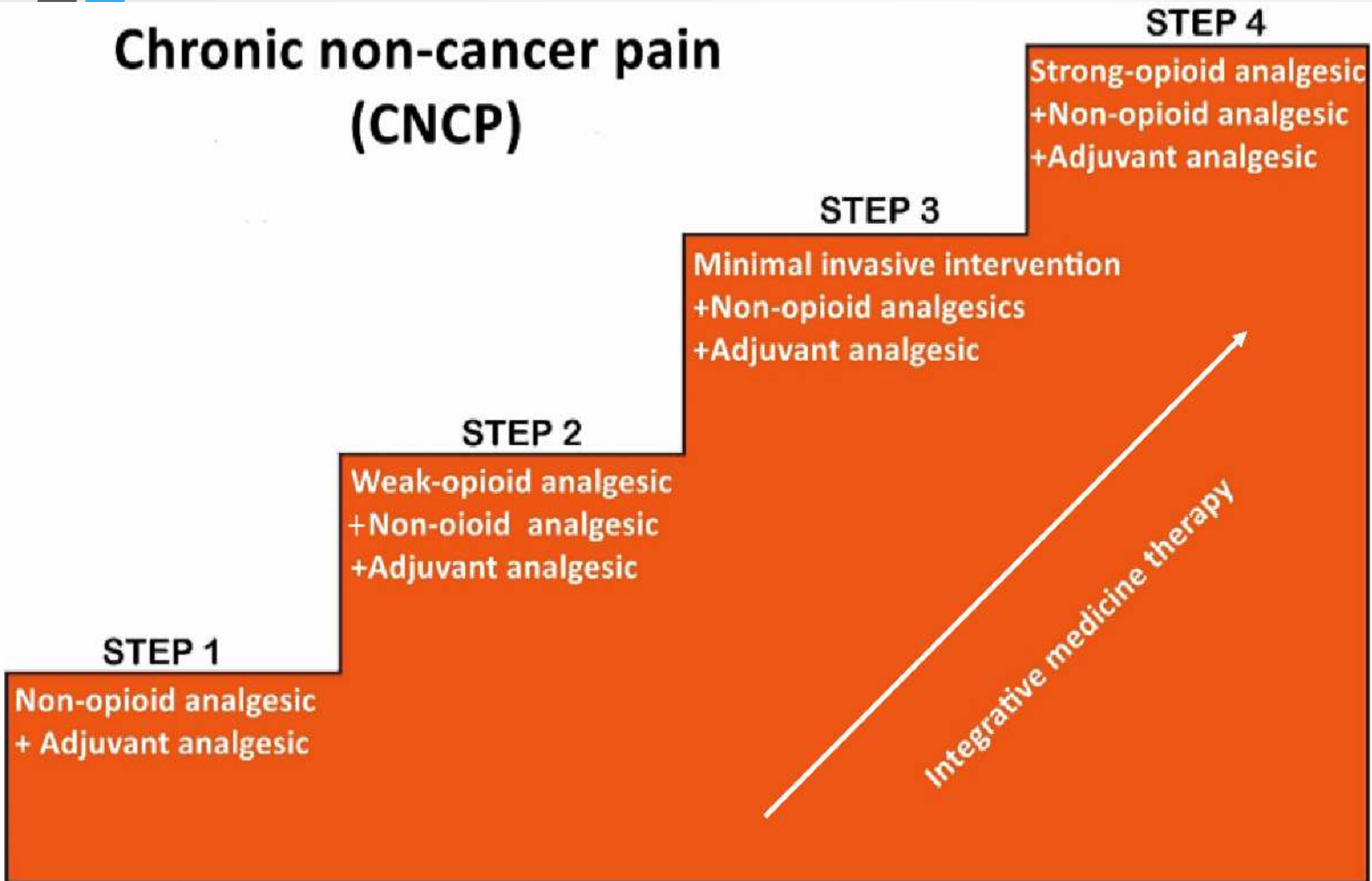
The WHO Analgesic ladder (1986)



[*Examples of adjuvants include corticosteroids, antidepressants, hypnotics and anticonvulsants/antiepileptic agents.]

Four-step analgesic ladder (2020)

Chronic non-cancer pain (CNCP)



ANALGETIK OPIOID

“**OPIOID**” is a natural or synthetic drug that binds to opioid receptors producing agonist effects

- **Morfin, Codein** = plant opioid alkaloid, diekstrak dr Papaver somniferum – narcotic analgetic – supresi neurotransmisi pd pusat sensasi nyeri di sumsum tulang belakang dan otak – nyeri viseral dan nyeri berat
- **Papaverin** – antispasmodic
- **Noscipin** – cough suppressant

RESEPTOR OPIOID : **Mu (μ), Sigma (δ), Kappa (κ) & Delta (δ)**

- Endogenous peptide=endorphin, dynorphin, enkephalin, dan peptide opioid endogen (nociceptin, orphanin)
- Reseptor : Mu opioid peptide (MOP), Delta opioid peptide (DOP), Kappa opioid peptide (KOP), Sigma (bukan resept opioid peptida sejati) ;
- Nociceptin opioid peptide (NOP) – ligan =nociceptin, orphanin-tdk ada afinitas thd MOP, DOP, KOP
- Nalokson = antagonis rec opioid (tdk ada afinitas dg NOP)
- Recept opioid tersebar (SSP, GIT, kardiovask, sist imun)
- Sangat efektif
- Efek samping sering

ANALGETIK OPIOID

Aktivasi Reseptor μ -Opioid (G-prot couple rec) menyebabkan :

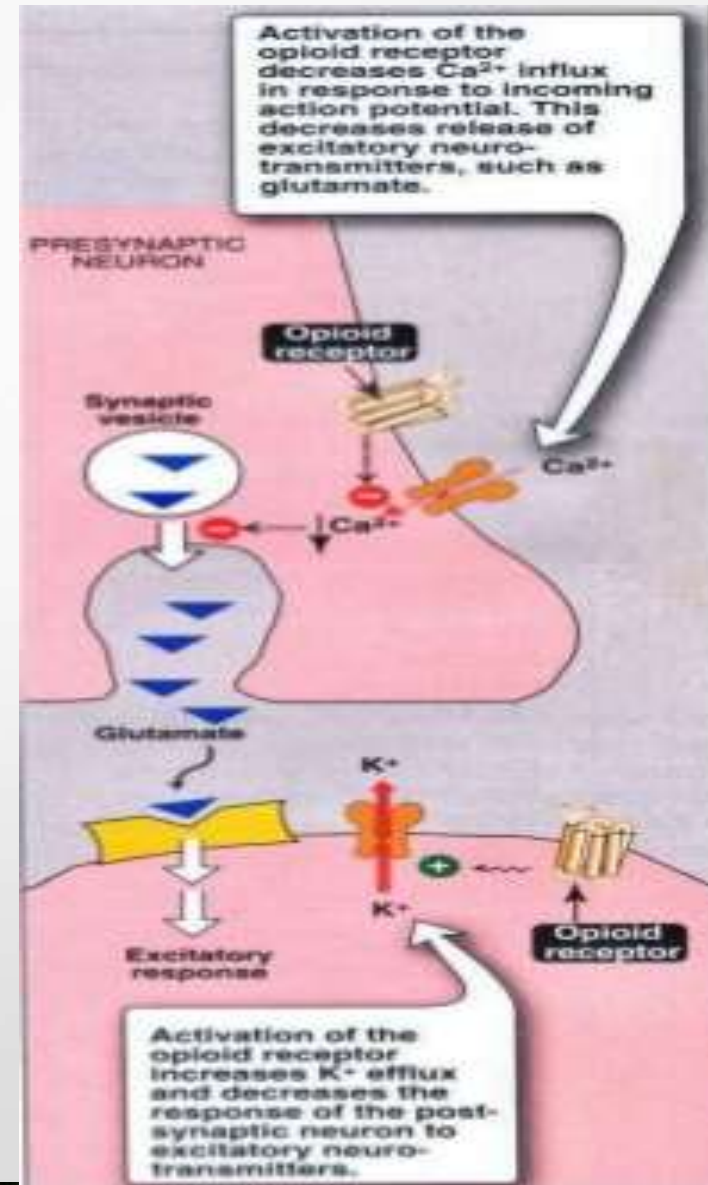
A. Hamb adenilat siklase

- Hamb influk Ca^{+}
- Release neurotransmitter terhambat, mis glutamat

B. Me \uparrow konduktansi ion K

- Hiperpolarisasi
- Aksi potensial terhambat

C. Blok kanal Ca



ANALGETIK OPIOID

Aktivasi reseptor Mu :

- a. Menghamb ascending pain pathway (dorsal horn of the spinal cord, brainstem, thalamus and cortex.
- b. Mengaktivasi inhibitory descending pain pathway (brainstem)

Reseptor μ ada 2 subtype :

μ_1 - di SSP -efek analgetik dan euphoria

μ_2 – SSP dan perifer (GIT) –
depresi nafas , konstipasi

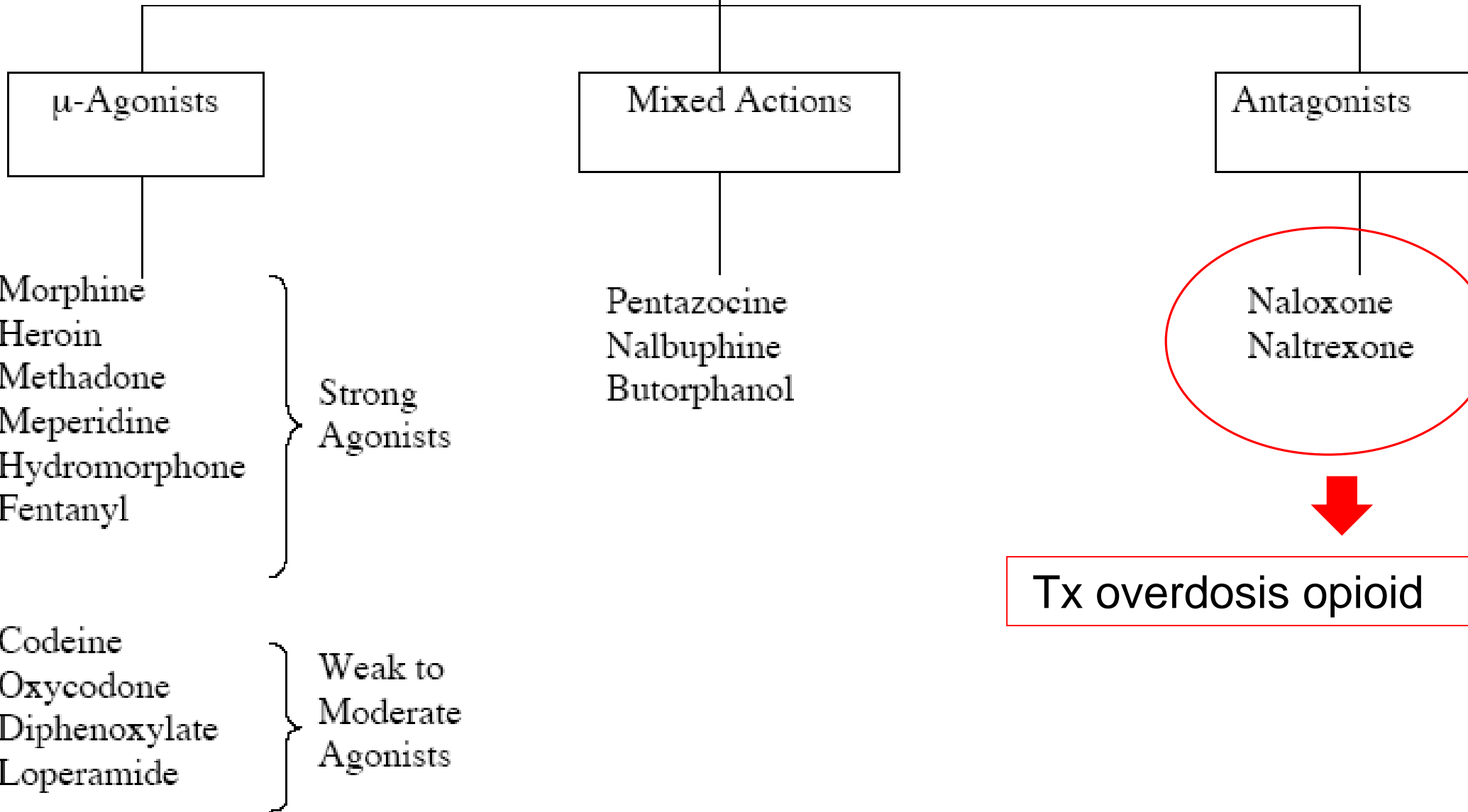
Delta dan Kappa opioid
receptor

- Mis oxycodone

	Mu (μ)	Delta (δ)	Kappa (κ)	Sigma (σ)*
Pain	Strong analgesic effects at spinal and supraspinal (brain) level, as well as peripherally	Spinal analgesic effects	Peripheral and some spinal analgesic effects	
Mood and consciousness	Euphoria, sedation		Sedation, dysphoria	Dysphoria, hallucinations and nightmares
Breathing	Suppresses the respiratory centre (also suppresses the cough centre)	Some respiratory depression		Stimulation, tachypnoea
Blood pressure and pulse rate	May cause bradycardia			Increases blood pressure and pulse rate
Gastrointestinal tract	Smooth muscle contraction with spastic paralysis of the small intestine, leading to constipation; increased biliary sphincter tone**; also causes nausea and vomiting	Reduced gastrointestinal motility		
Other	Miosis, physical dependence			Mydriasis, hypertonia

Opioid Drugs

Opioid vs. Opiate



Tx overdose opioid

EFEK FARMAKOLOGIS MU- OPIOID

- **Sedation and anxiolysis**
 - Drowsiness and lethargy
 - Apathy
 - Cognitive impairment
 - Sense of tranquility
- **Depression of respiration**
 - Main cause of death from opioid overdose
 - Combination of opioids and alcohol is especially dangerous
- **Cough suppression**
 - Opioids suppress the “cough center” in the brain
- **Pupillary constriction**
 - pupillary constriction in the presence of analgesics is characteristic of opioid use

Opioid untuk nyeri akut dan kronik

Drug	Formulations available	Oral bioavailability	Half-life (immediate-release formulation) *	Clearance mechanism	Comments
morphine	immediate release (oral, parenteral) sustained release 12 hourly or 24 hourly (oral)	30%	3 hours	liver metabolism (mainly glucuronidation) important active metabolites (M3G, M6G) renally cleared	active metabolites are problematic in renal failure
oxycodone	immediate release (oral, parenteral) sustained release 12 hourly (oral)	70%	2.5 hours	liver metabolism (mainly CYP) some active metabolites with small contribution to effect approximately 20% of dose renally cleared	also available combined with naloxone (sustained release only) for management of opioid bowel dysfunction
hydromorphone	immediate release (oral, parenteral) sustained release 24 hourly (oral)	30%	2.5 hours	liver metabolism (mainly glucuronidation) active metabolite H3G is both implicated in toxicity and renally cleared	significantly more potent than morphine and oxycodone
fentanyl	immediate release (buccal/oral, parenteral) sustained release (transdermal)	50% (lozenge)	3 hours (following an intravenous dose)	liver metabolism (mainly CYP3A4) no active metabolites	lowest dose patch (12 microgram/hour) is not suitable for opioid-naïve patients as it can cause serious toxicity suitable choice in renal failure
methadone	immediate release (oral, parenteral)	40–90%	15–60 hours	liver metabolism (mainly CYP) no active metabolites	due to complex pharmacokinetics should be commenced under specialist supervision

Drug	Formulations available	Oral bioavailability	Half-life (immediate-release formulation) *	Clearance mechanism	Comments
buprenorphine	immediate release (sublingual, used for opioid maintenance treatment) sustained release (transdermal)	30% (sublingual route)	35 hours (following sublingual administration)	liver metabolism (mainly CYP) active metabolites	a partial mu agonist that may induce withdrawal in an opioid-tolerant patient
codeine	immediate release (oral, parenteral)	60%	3 hours	liver metabolism (mainly glucuronidation) variable proportion of dose converted to morphine	not suitable for chronic pain significant variability in analgesic response between patients
tramadol	immediate release (oral, parenteral) sustained release (oral)	70%	6 hours	liver metabolism active metabolite is important for therapeutic effect	risk of serotonin toxicity in overdose or in combination with other serotonergic drugs

* half-lives are approximate as published values vary depending on the study and the exact formulation used

M3G morphine-3-glucuronide M6G morphine-6-glucuronide CYP cytochrome P450 H3G hydromorphone-3-glucuronide

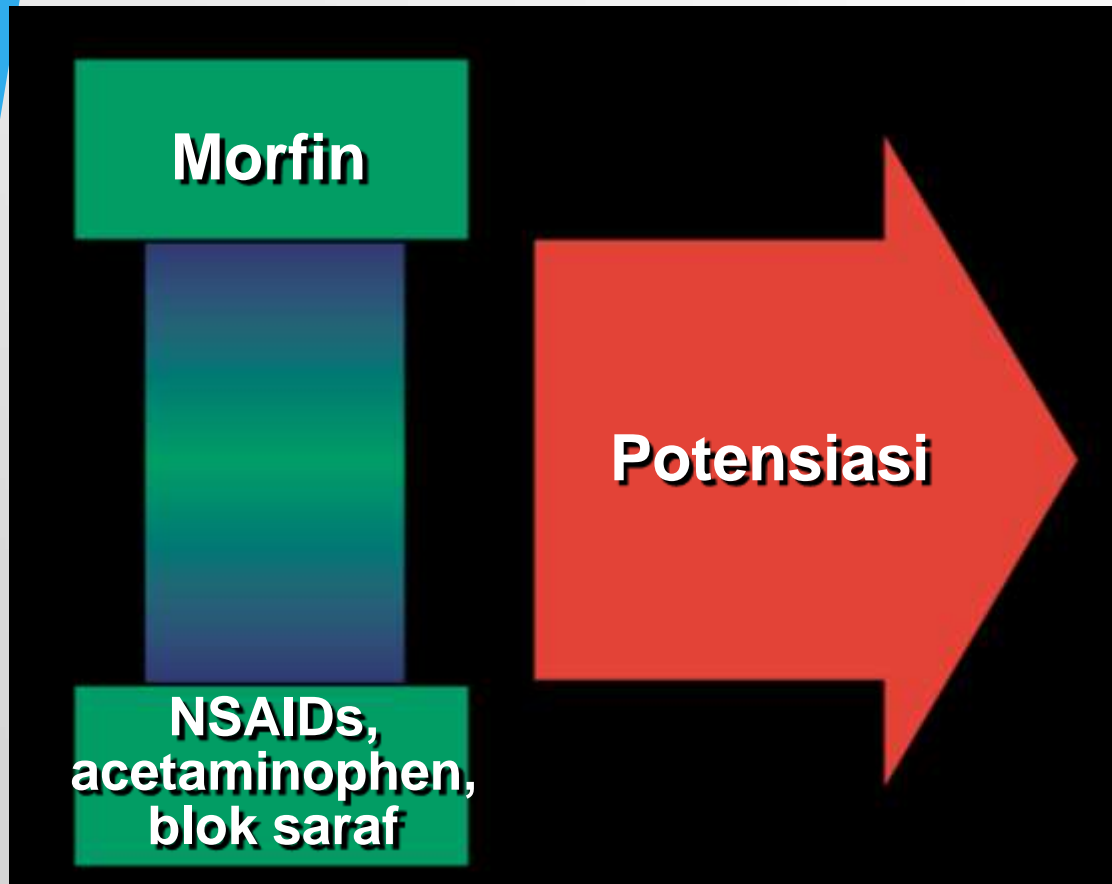
EFEK FARMAKOLOGIS ANALGETIK OPIOID

- **Nausea and vomiting**
 - Stimulation of receptors in an area of the medulla called the chemoreceptor trigger zone causes nausea and vomiting
 - Unpleasant side effect, but not life threatening
- **Gastrointestinal symptoms (constipation)**
 - Opioids relieve diarrhea as a result of their direct actions on the intestines
- **Urine Retention**
- **Other effects**
 - Opioids can release histamines causing itching or more severe allergic reactions including bronchoconstriction
 - Opioids can affect white blood cell function and immune function

Kombinasi

- Utk meningkatkan effikasi
 - Codein + non-opioid (ibuprofen / parasetamol)
 - Codein + doxylamine
- Utk mengurangi efek samping
 - Buprenorphine one + naloxone (antagonist opioid receptor)
 - Tx maintenance pd addiksi opioid
 - Oxycodone + naloxone
 - Nyeri berat kronik dan tx disfungsi bowel
 - Nalokson oral-low bioavaibility, antagonis efek opioid pd GIT (mengurangi resiko konstipasi), dan minimal efek pd SSP

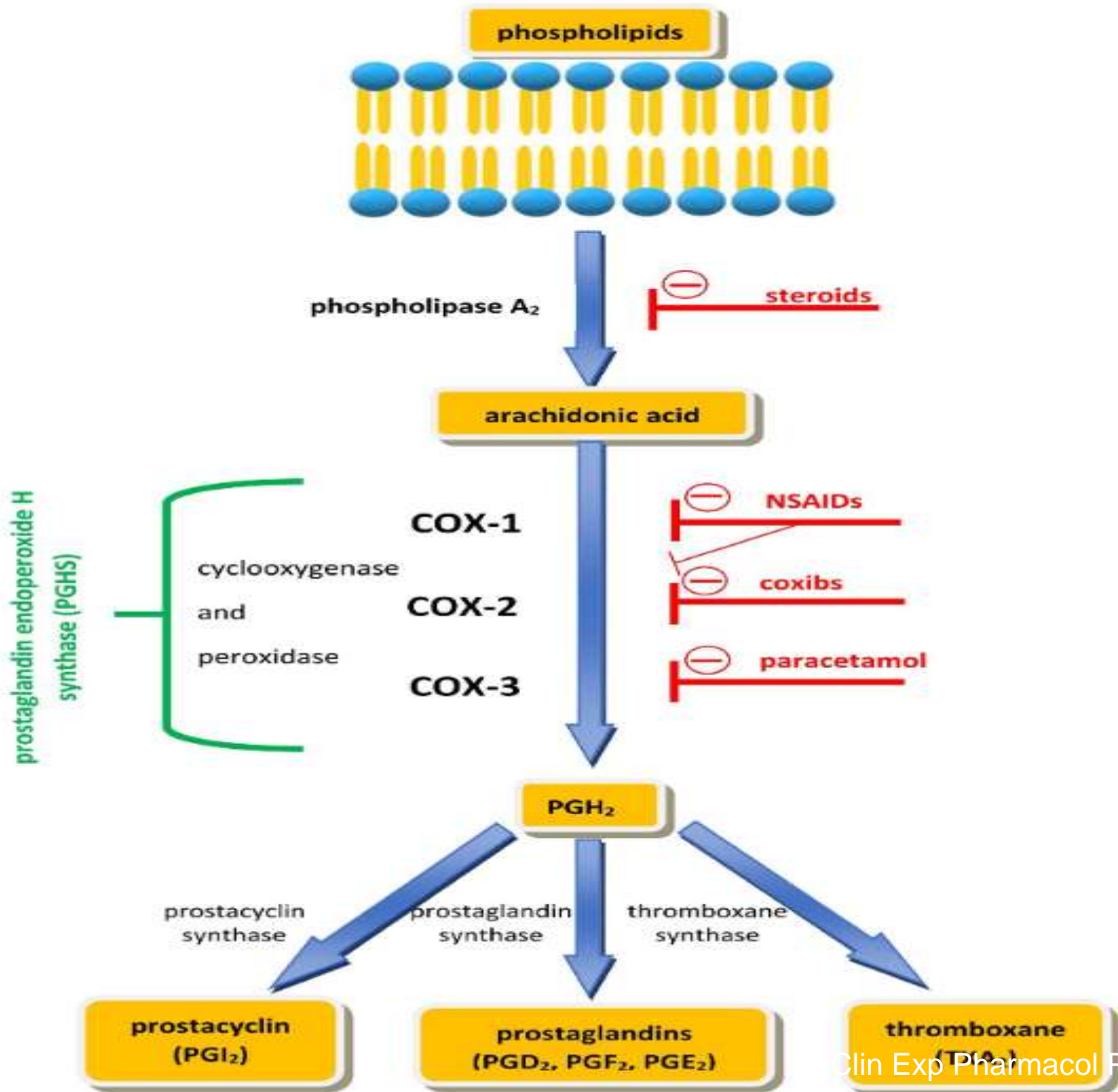
Multimodal Analgesia



- Pengurangan dosis tiap analgesik
- Meningkatkan antinociception karena efek sinergistik
- Mengurangi efek samping tiap obat



ANALGESIK NON OPIOID



ANALGESIC NON OPIOID DRUGS

- Acetaminophen
- NSAID
 - Non selective COX inhibitor
 - Salicylic acid (aspirin)
 - Acetic acid (indomethacin, ketorolac, diclofenac)
 - Propionic acid (ketoprofen)
 - Anthranic acid (mefenamat)
 - Enolic acid (piroxicam)
 - Selective COX – 2 Inhibitor
 - Rofecoxib
 - Celecoxib
 - Etedolac

PARASETAMOL/ASETAMINOFEN

Regular doses^{244,245}

Gastrointestinal complaints²⁴⁷

Hypersensitivity reactions,²⁴⁹ angioedema²⁵⁰

Kidney damage²⁵²

Gastrointestinal bleeding (doses > 2 g taken chronically)²⁵³

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)^{254,255}

Agranulocytosis,²⁵⁶ anaemia,²⁵⁷ thrombocytopenia²⁵⁸

Small increased of systolic blood pressure,²⁶⁰ hypertension²⁶¹

Toxic doses²⁴⁶

Serious liver damage and acute liver failure²⁴⁸

Nausea, vomiting, sweating²⁵¹

Pain in the right hypochondrium²⁵¹

High increase of aminotransferases (above 10 000 U/L) and the international normalized ratio (INR) ≥ 4.0 ²⁴⁶

Nausea and hepatic encephalopathy²⁴⁶

Acute (tubular) kidney injury and skeletal muscle cytolysis²⁵⁹

Thrombocytopenia²⁶²

Note: The side effects may coexist or occur separately. Regular doses: up to 4 g/d in adults or up to 60 mg/kg/d in paediatric patients show slight adverse effects.^{244,245} Toxic doses: intake by health adults above 4 g/d of paracetamol or lower doses in combination with alcohol consumption.²⁴⁶

ANALGESIK NON-OPIOID NON-NSAID

Acetaminophen

Tramadol

Mekanisme kerja

hamb sintesa PG
hipotalamus,

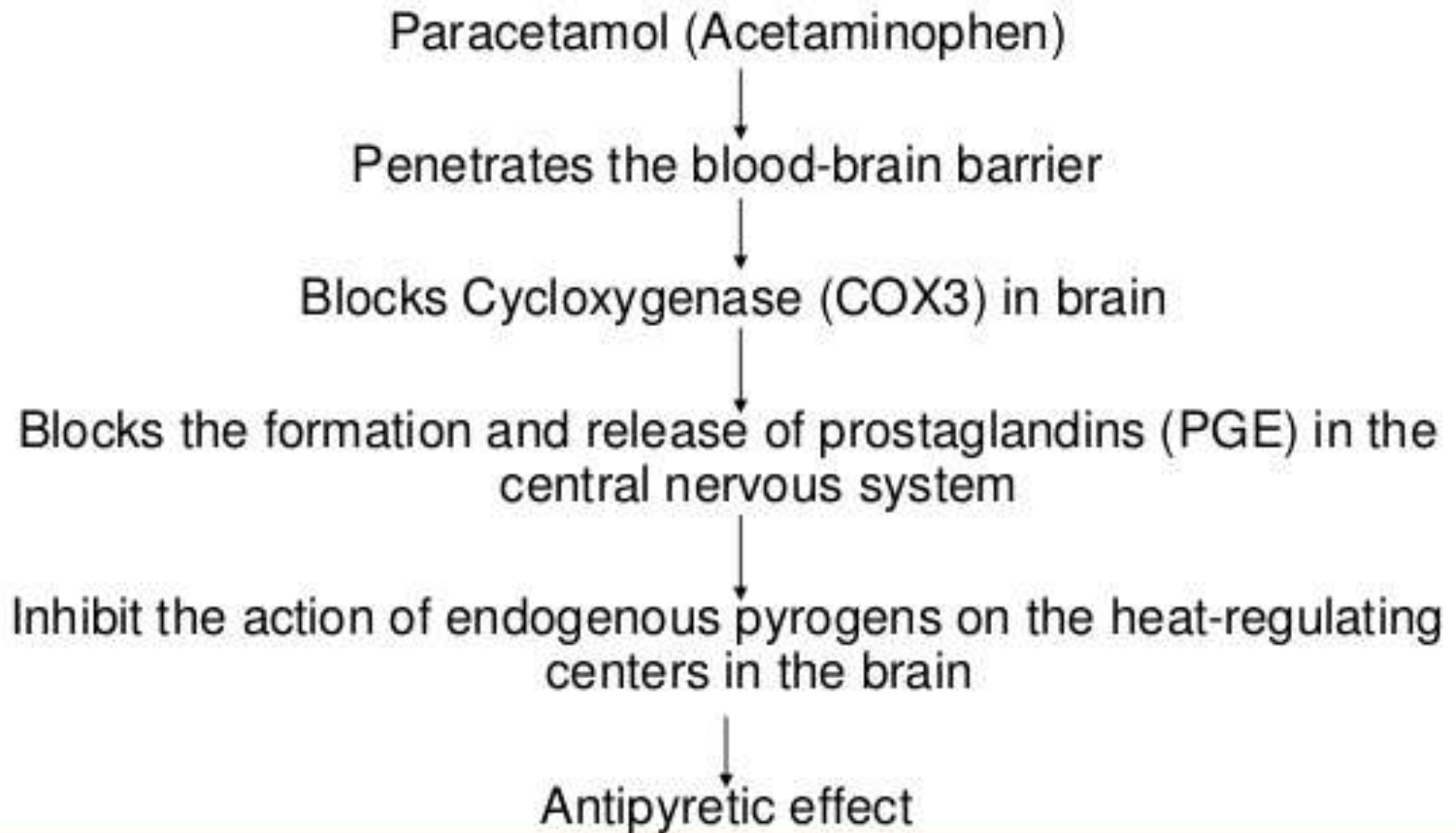
- sintetik *weak μ -opioid*
- inhibisi re-uptake
norepinephrine dan
serotonin (5-HT₃)

Efek samping

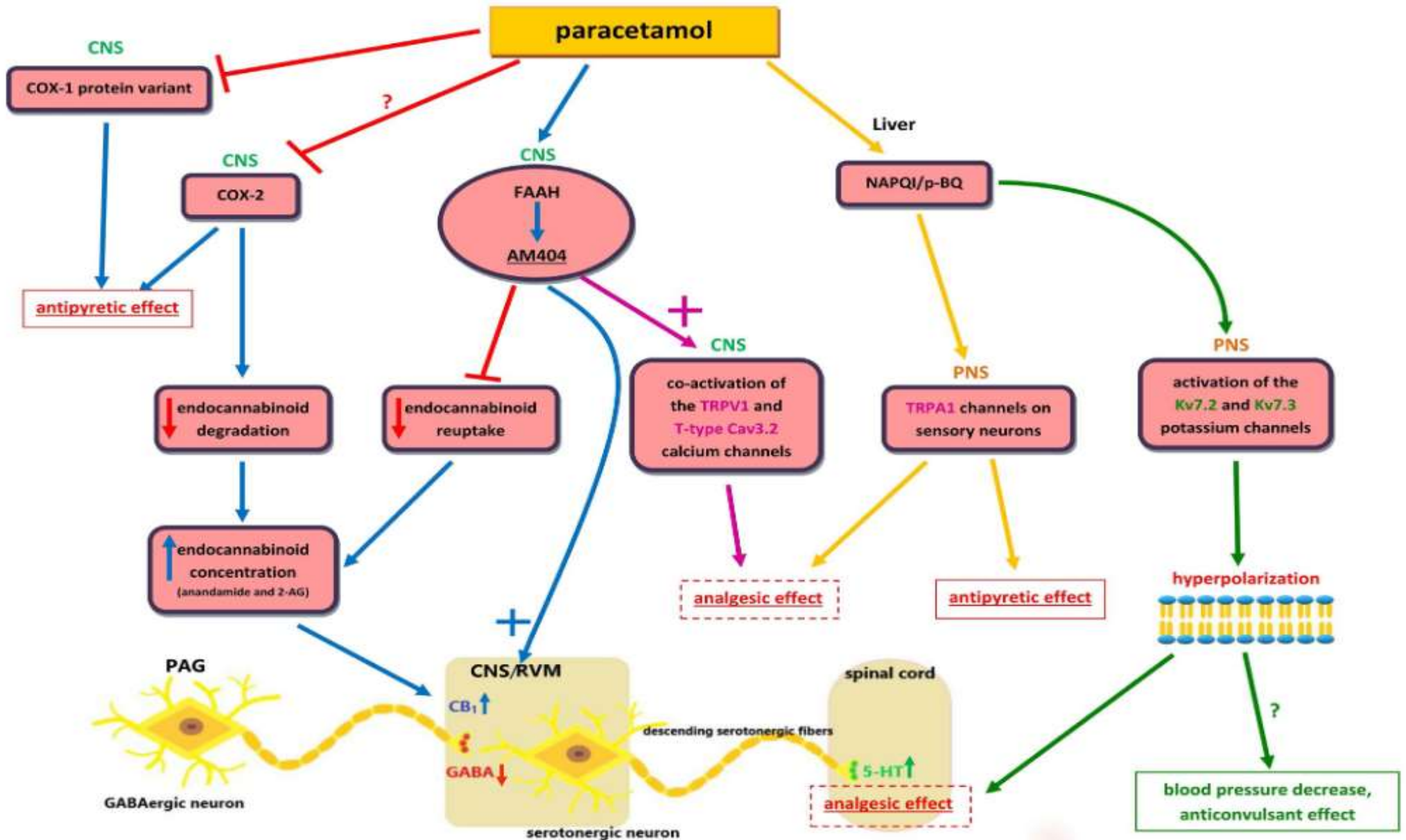
Hepatotoksik

Opioid-like effects

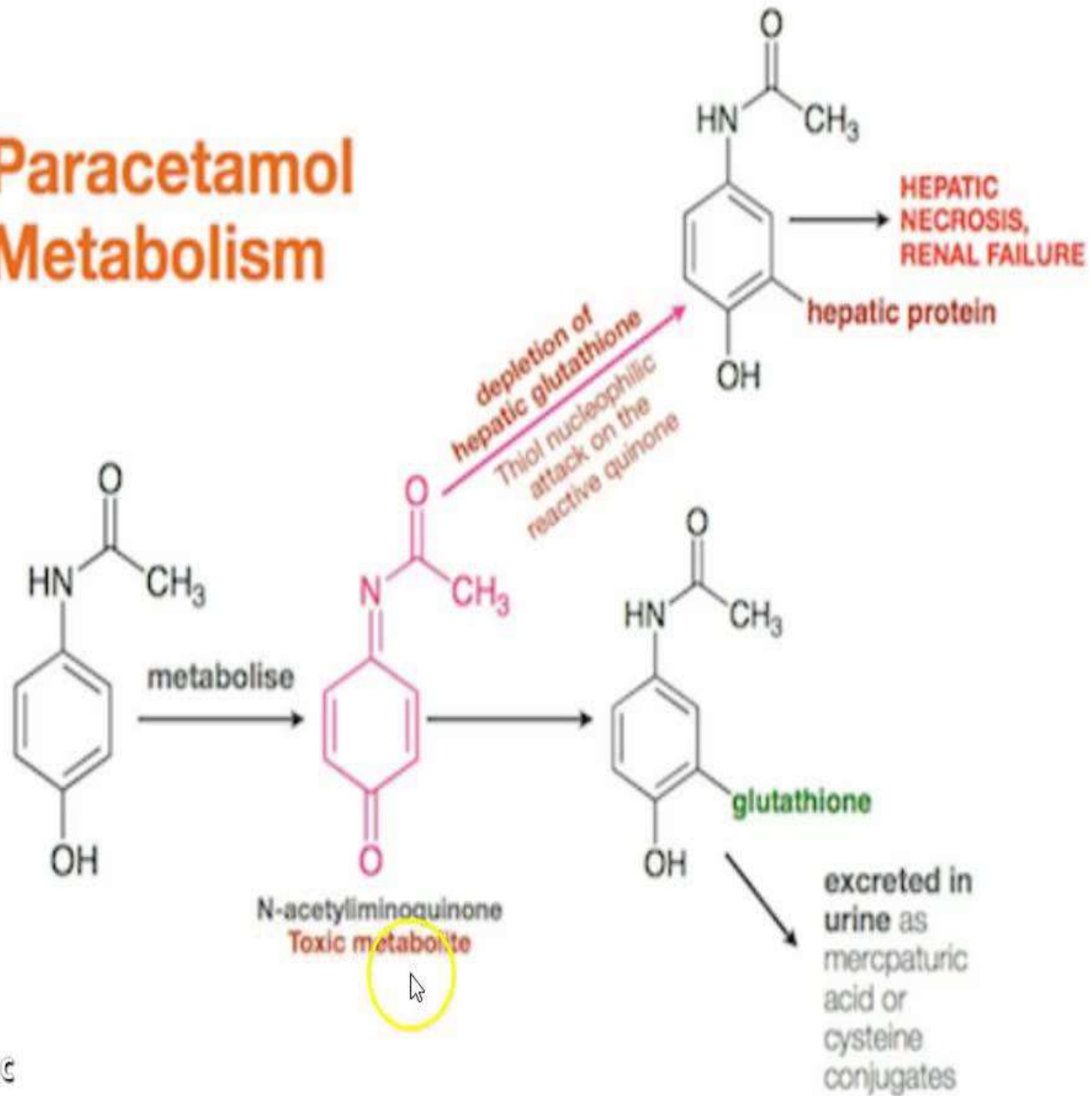
Mechanism of action of Paracetamol Acetaminophen



Farmakodinami Parasetamol



Paracetamol Metabolism





NSAID

**(NON STEROIDAL ANTI INFLAMMATORY
DRUG)**

OBAT AINS

ASAM KARBOKSILAT

ASAM ENOLAT

Asam Asetat

Derivat Asam Salisilat

Derivat Asam Propionat

Derivat Asam Fenamat

Derivat Pirazolon

Derivat Oksikam

- * Aspirin
- * Benorilat
- * Diflunisal
- * Salsalat

- * As. tiaprofenat
- * Fenbufen
- * Fenoprofen
- * Flurbiprofen
- * Ibuprofen
- * Ketoprofen
- * Naproksen

- * As. mefenamat
- * Meklofenamat

- * Azapropazon
- * Fenilbutazon
- * Oksifenbutazon

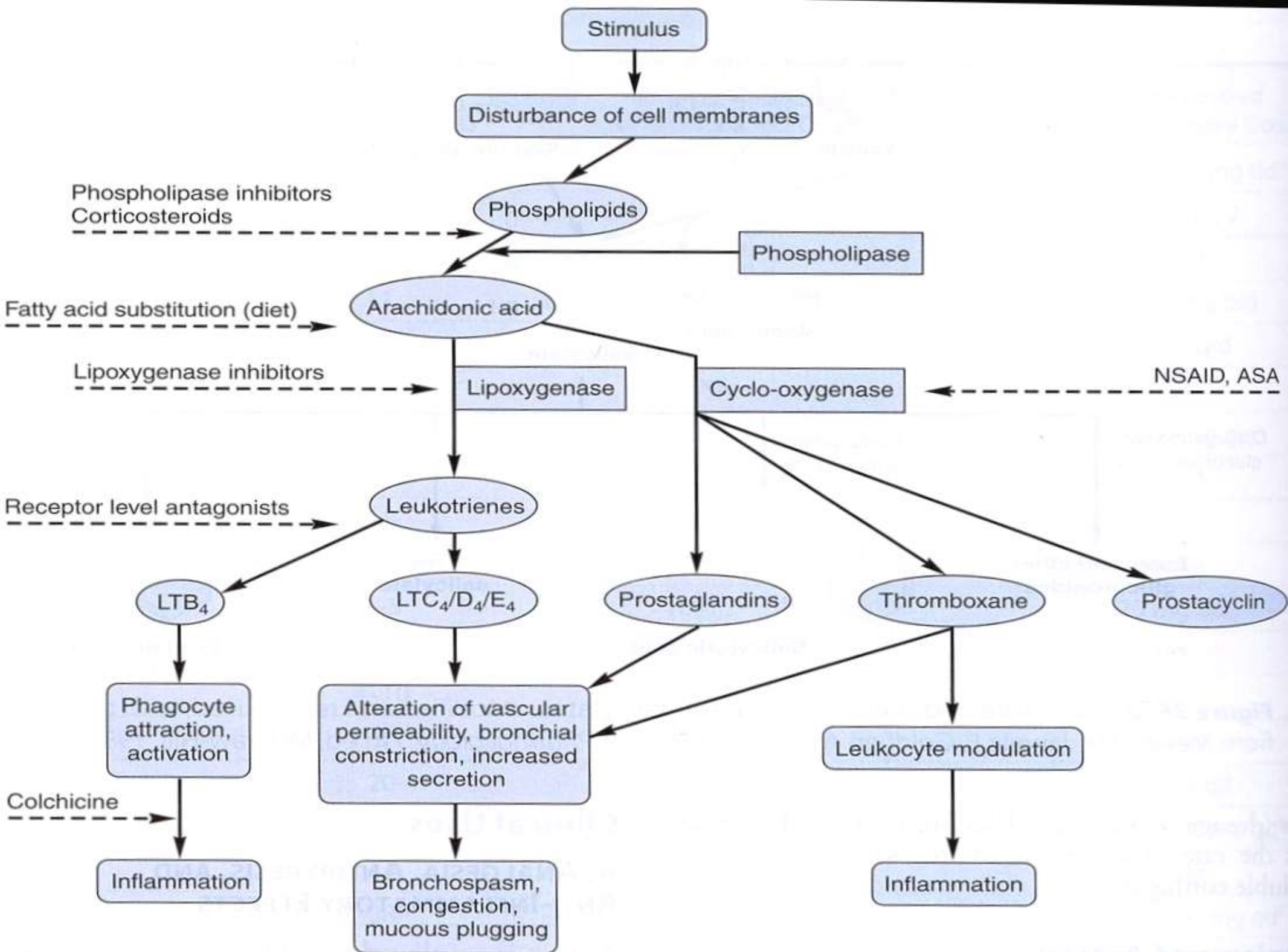
- * Piroksikam
- * Tenoksikam

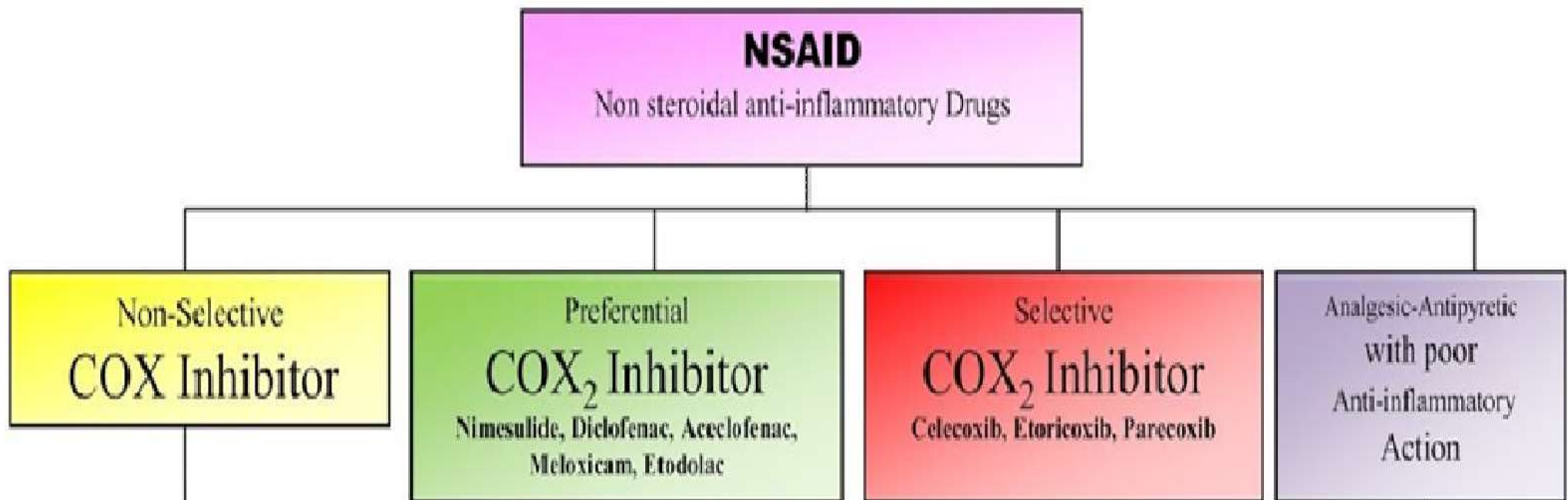
Derivat Asam Fenilasetat

Derivat Asam Asetat-inden / indol :

- * Diklofenak
- * Fenklofenak

- * Indometasin
- * Sulindak
- * Tolmetin





Category	Example
Salicylates	Aspirin
Acetic acid derivative	Indomethacin , Nabumetone, Ketorolac,
Pyrazolone derivative	Oxyphenbutazone, Phenylbutazone
Propionic acid derivative	Ketoprofen, Flurbiprofen, Ibuprofen , Naproxen,
Fenamate	Mephenmic acid
Enolic acid derivative	Piroxicam, Tenoxicam

Example
Paracetamol (Acetaminophen)
Metamizol, Propiphenazone
Nefopam

Less GI side effects

More GI side effects

Acetosal
Ketorolac

Indomethacin
Piroxicam

Ibuprofen
Ketoprofen

Diclofenac
Meloxicam
Nimesulide

COXIB

**COX-1
selective
inhibitor**

preferentially
**COX-1
selective
inhibitor**

**non-
selective
COX
inhibitor**

preferentially
**COX-2
selective
inhibitor**

**COX-2
selective
inhibitor**

anti-inflammatory

analgesic

log (IC₈₀ ratio COX-2/COX-1)

3
2
1
0
-1
-2
-3

Ketorolac

Flurbiprofen

Suprofen

Ketoprofen

Indometacin

Aspirin

Naproxen

Tolmetin

Ibuprofen

Ampyrone

Fenoprofen

COX-1 selective

Zomepirac

Niflumic acid

Sodium salicylate

Diflunisal

Piroxicam

Tomoxiprol

Meclofenamate

Sulindac

Diclofenac

<5-fold COX-2 selective

5-50-fold COX-2 selective

>50-fold COX-2 selective

Nimesulide

Celecoxib

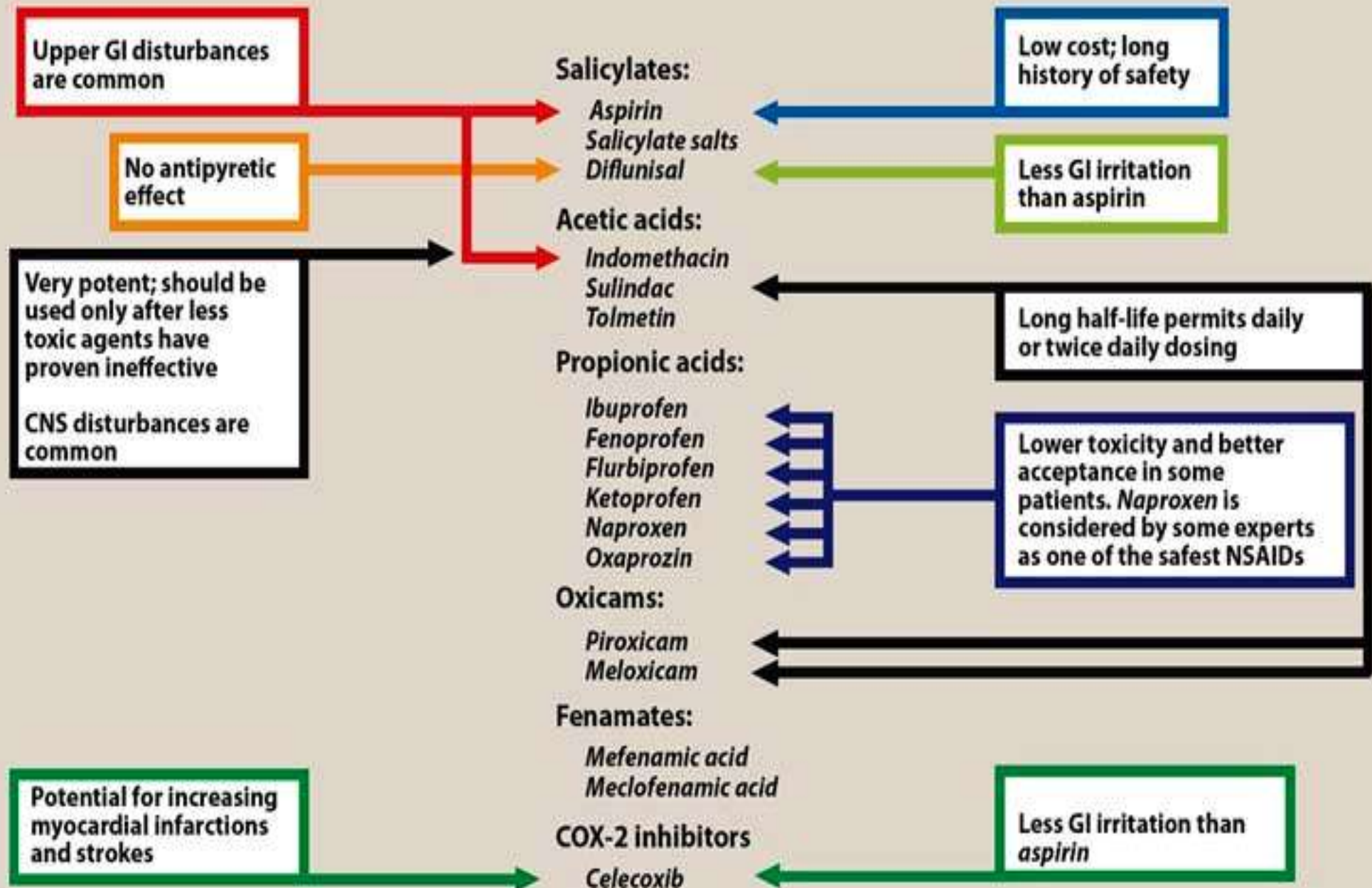
Meloxicam

Etodolac

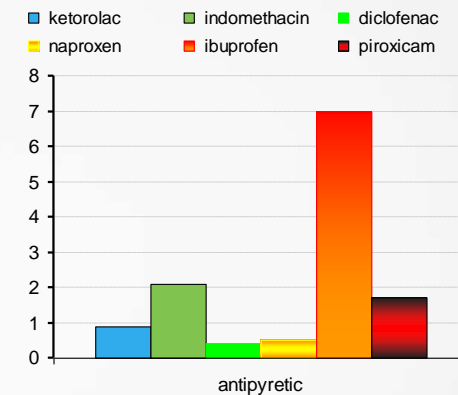
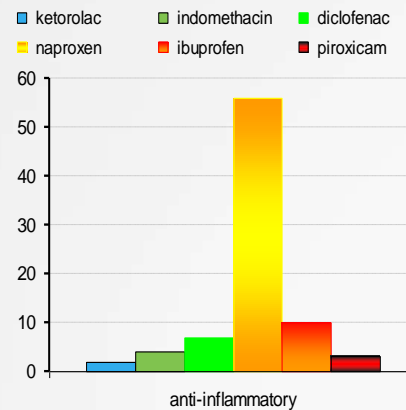
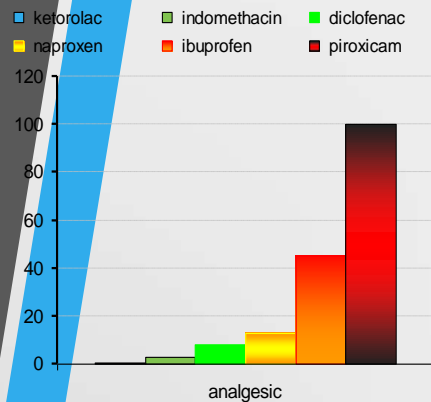
Rofecoxib

Therapeutic disadvantages of selected NSAIDs*

Therapeutic advantages of selected NSAIDs



Summary of analgesic, anti-inflammatory and antipyretic activity of NSAIDs (ED₅₀ in mg/kg)



NSAID	Analgesic	Anti-inflammatory	Antipyretic
ketorolac	0.7	2	0.9
indomethacin	3	4	2.1
diclofenac	8	7	0.4
naproxen	13	56	0.5
ibuprofen	45	10	7
piroxicam	100	3	1.7
tenoxicam	100	5	1.7
aspirin	228	162	18

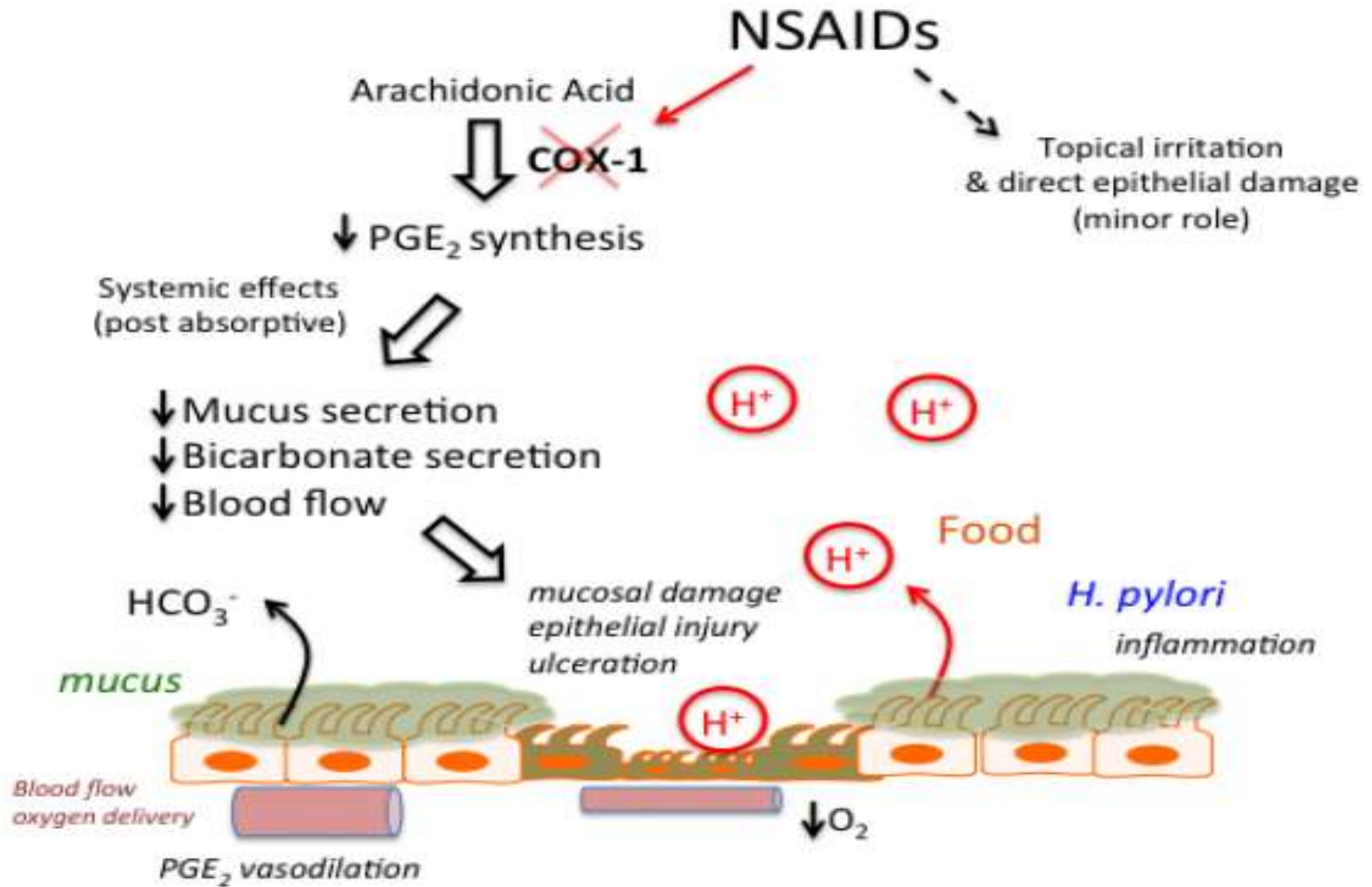
3 KELAS NSAID BDS MEKANISME KERJA

1. Nonselective COX₂-inhibitor
 - antiinflammatory effects, reversible antiplatelet (5-95%)
 - gastrointestinal, bronchial and renal side effects
 - ibuprofen, ketoprofen, ketorolac, mefenamic acid, indomethacin
2. Selective COX₂-inhibitor
 - antiinflammatory effects is higher than non-selective
 - less bleeding, lack platelet inhibition, minimal gastrointestinal, bronchial and renal side effects
 - increased cardiovasc event (myocard infarction, stroke)
 - rofecoxib (CV toxicity), celecoxib, diclofenac, meloxicam
3. Aspirin
 - irreversible inhibit COX1 & COX2
 - low doses : suppress platelet COX-1 activity (95%)

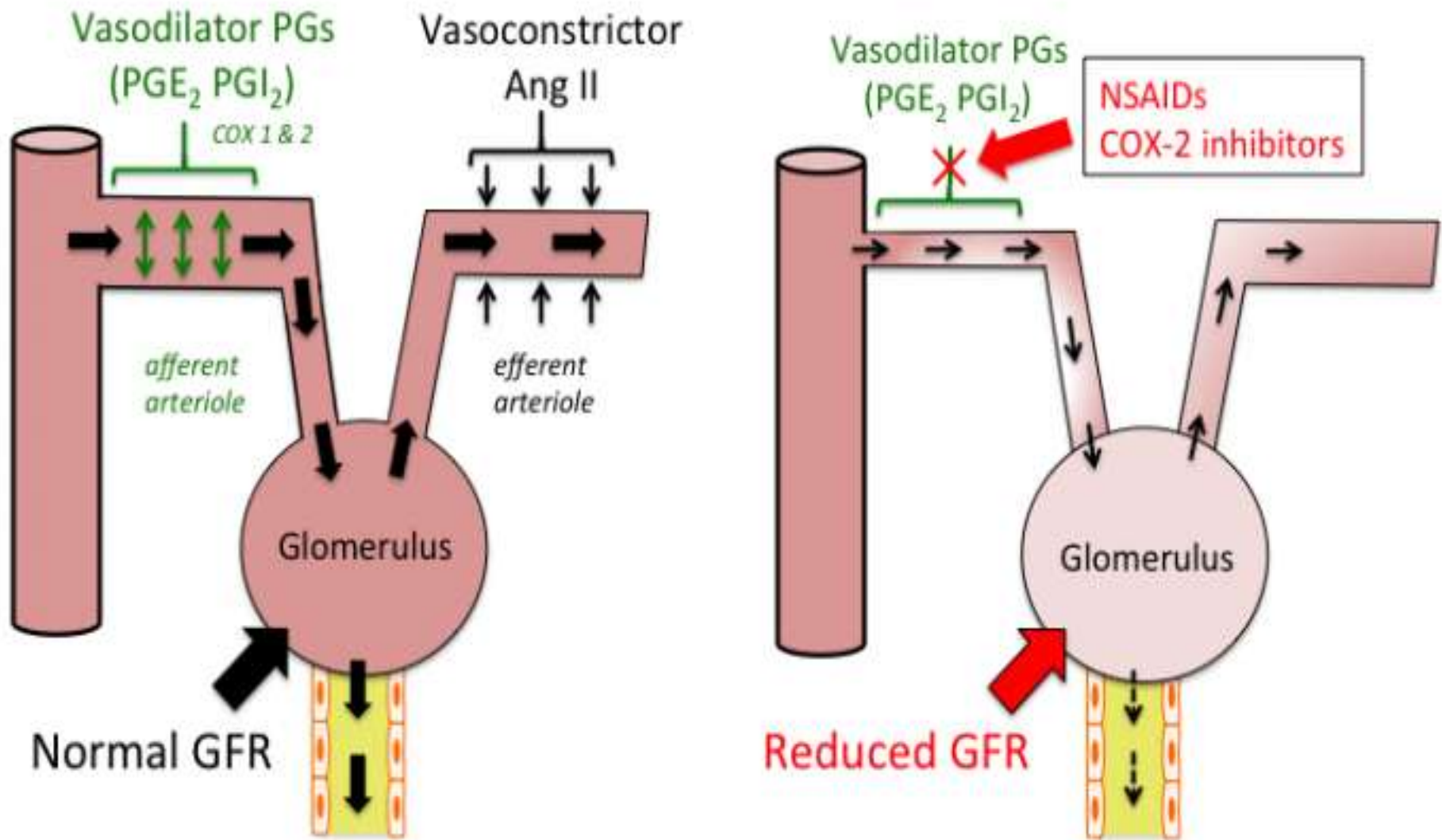
Table1: Adverse effects of NSAIDs on various systems

Cardiovascular side effects	<ul style="list-style-type: none">➤ Edema➤ Hypertention➤ Congestive heart failure➤ Myocardial infarction➤ Stroke and other thrombotic events
Gastrointestinal toxicity	<ul style="list-style-type: none">➤ Dyspepsia➤ Gastroduodenal ulcer➤ GI bleeding and perforation
Nephrotoxicity	<ul style="list-style-type: none">➤ Electrolytic imbalance➤ Sodium retention➤ Edema➤ Reduce glomerular filtration rate➤ Nephrotic syndrome➤ Acute interstitial nephritis➤ Renal papillary necrosis➤ Chronic kidney disease

Side effect : GI toxicity

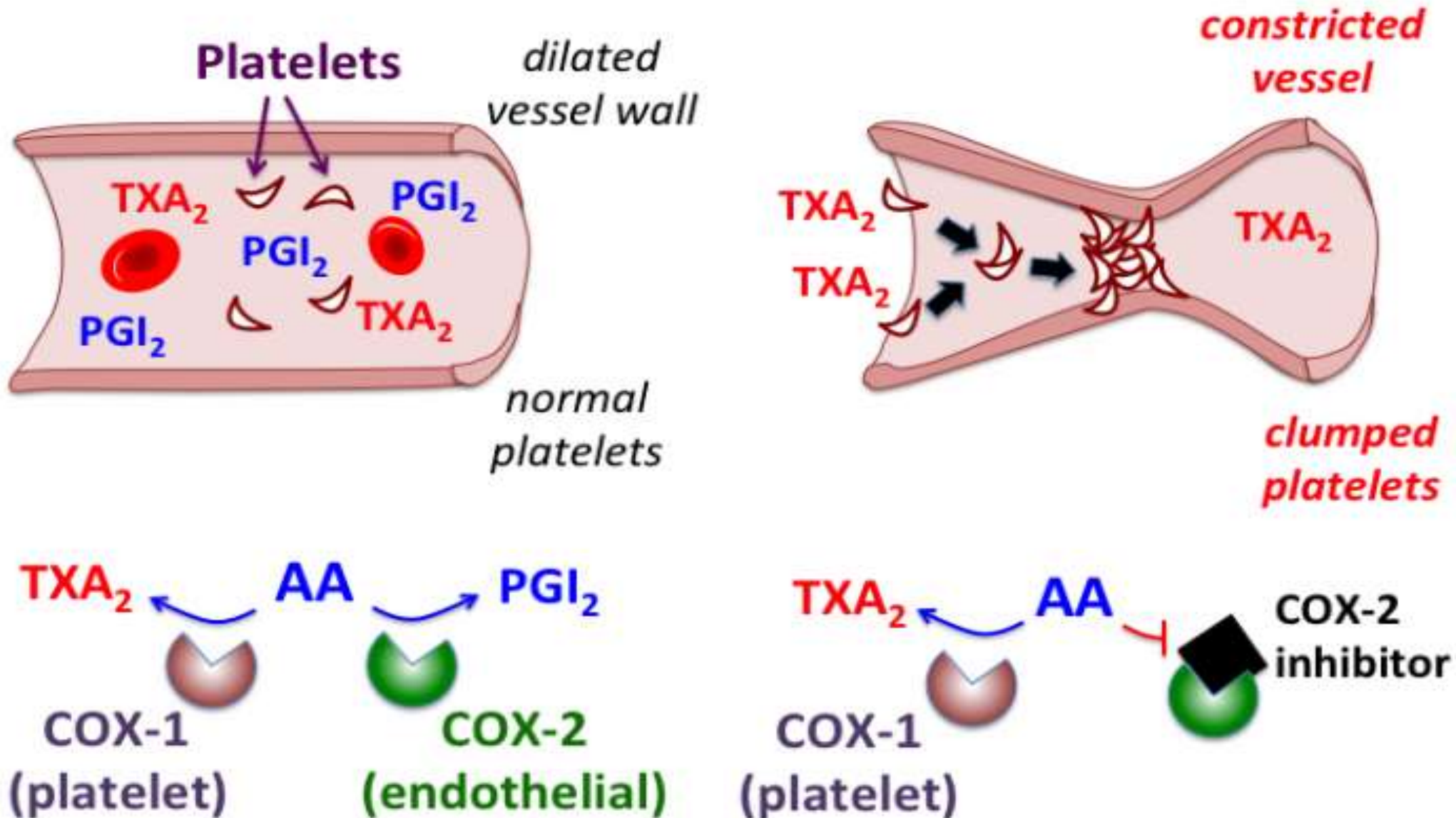


Side effect : Renal Toxicity



Selective COX-2 Inhibition & Enhanced CV Risk

(The Thromboxane/Prostacyclin Imbalance Hypothesis)





London, 27 June 2005
Doc. Ref. EMEA/207766/2005

For the other COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib and parecoxib), the Committee agreed that the available data show an increased risk of thrombotic adverse cardiovascular reactions, such as heart attacks and strokes. The CHMP confirmed its February 2005 finding of an association between duration and dose of intake and the probability of suffering such cardiovascular reactions. The Committee also confirmed that serious skin reactions occur with other COX-2 inhibitors, but have been reported at lower rates than with Bextra. In concluding its review, the CHMP recommended the following contraindications and precautions for these products:

- **Contraindications** stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- Additional or strengthened warnings to healthcare professionals and patients that hypersensitivity reactions and rare, but serious and sometimes fatal, skin reactions can occur with all COX-2 inhibitors. In the majority of cases these occur in the first month of use, and prescribers are warned that patients with a history of drug allergies may be at greater risk.

Medicaments	Interactions
Antiplatelets (aspirin, clopidogrel)	Risk of GI bleeding
Angiotensin-converting-enzyme inhibitor (ACEI) and Angiotensin Receptor Blockers (ARB)	Increases in blood pressure by attenuating antihypertensive effects
Beta blockers	Increases in blood pressure by attenuating antihypertensive effects
Calcium antagonists	Increases in blood pressure by attenuating antihypertensive effects
Corticosteroids	Increases risk of GI bleeding
Digitalis glycosides	Increase serum digoxin level
Diuretics	Increases in blood pressure by attenuating antihypertensive effects
Methotrexate	NSAIDs reduce renal excretion of methotrexate, causing ethotrexate toxicity.
Selective serotonin reuptake inhibitors (SSRIs)	Increases risk of GI bleeding
Warfarin and other anticoagulants	Increases risk of GI bleeding

High risk	History of previous complicated ulcer, especially recent Multiple (>2) risk factors
Moderate risk (1-2 risk factors)	Age >65 years High dose NSAID therapy A previous history of uncomplicated ulcer Concurrent use of aspirin (including low-dose), corticosteroid or anticoagulant
Low risk	No risk factors

American Medical Journal 3 (2): 115-123, 2012

Table 5: Summary of recommendations for prevention of NSAIDs-related ulcer complications (adapted from Lanza *et al.*, 2009)

	GI risk		
	Low	Moderate	High
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	SAID + PPI or misoprostal	Alternative therapy if possible or COX-2 inhibitor + PPI or misoprostal
High CV risk	Naproxen + PPI or misoprostal	Naproxen + PPI or Misoprostal	Avoid NSAIDs and COX-2 inhibitors use alternative therapy



ANTIPYRETIC

DEMAM / PANAS

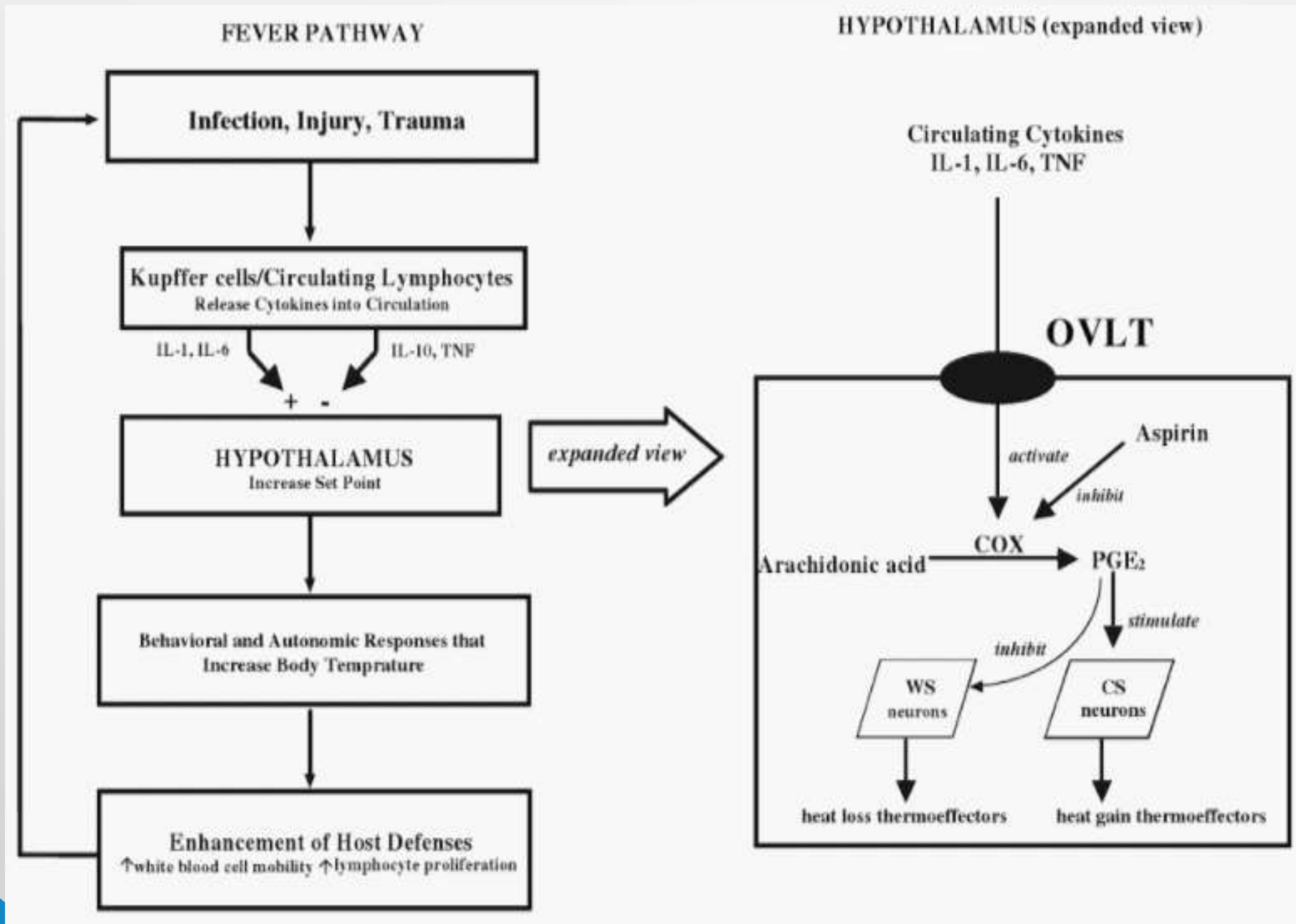
Suhu tubuh diatur oleh keseimbangan produksi dan hilangnya panas oleh hipotalamus (normal termostat mengatur pd setpoint 37° C)

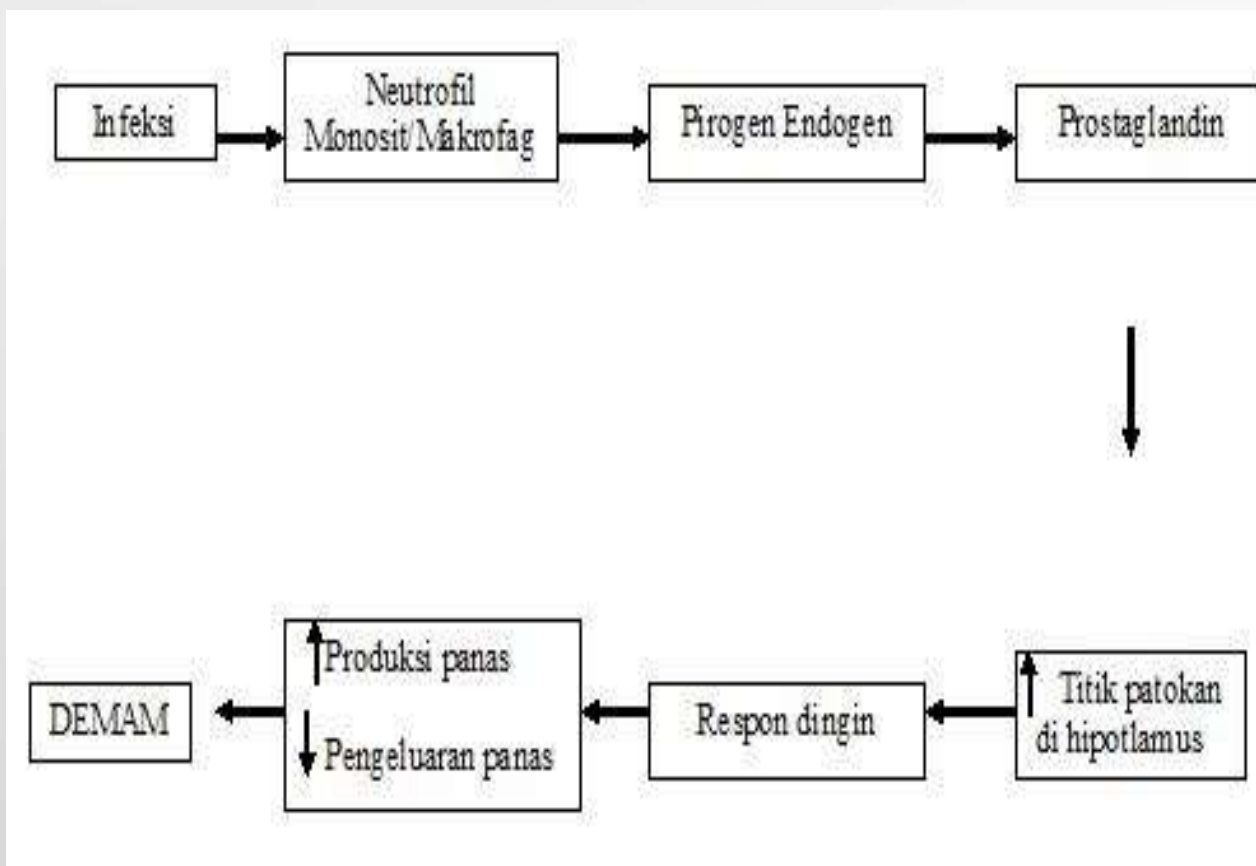


termoregulator

Demam : Ada gangguan keseimbangan pengaturan panas akibat pelepasan zat pirogen (sitokin → IL-1 , memicu peningkatan PG di hipotalamus)

FEBRIS





Antipyretic analgesics

Paracetamol

Acetanilide

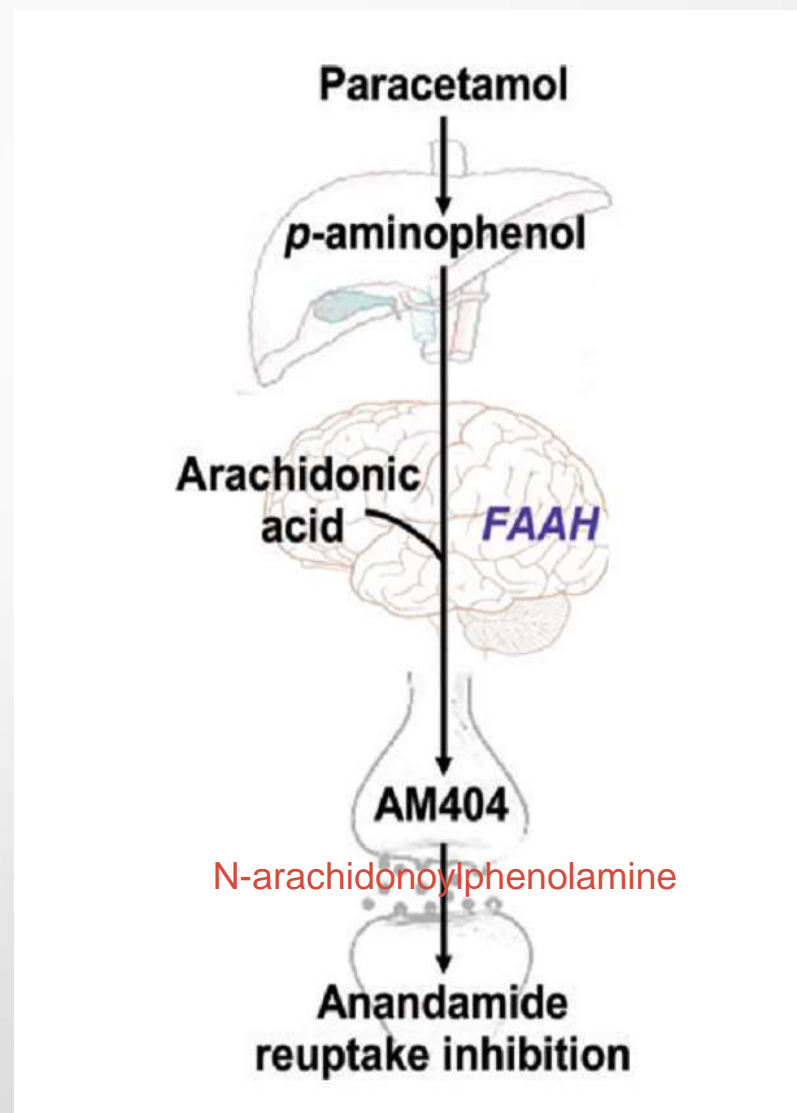
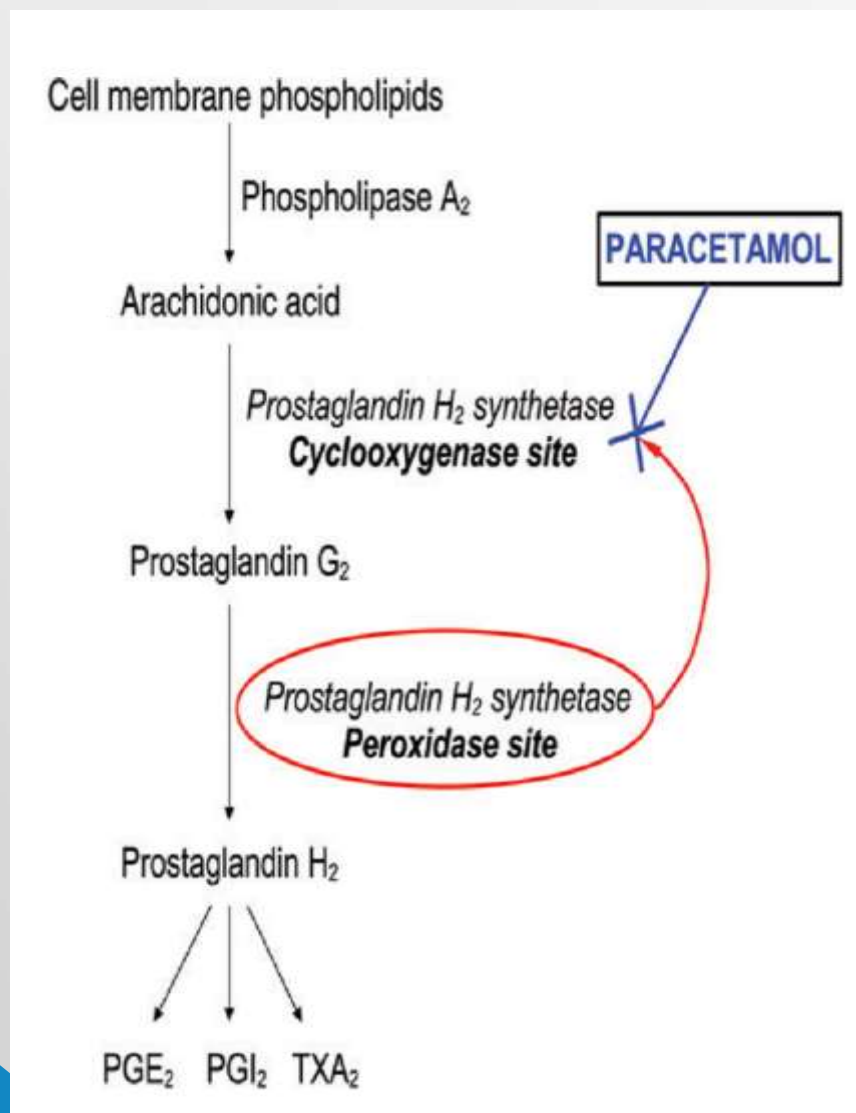
Phenacetin

Antipyrine

Amidopyrine

Dipyrrone

Mechanism of action Paracetamol



MECHANISM OF ACTION

Analgesic

- **Centrally**
- inhibition of COX enzymes in CNS
- **peripherally**
 - Anti-Inflammatory action

Antipyretic

- **Centrally**
- inhibition of COX enzymes
 - in CNS
- inhibition of interleukin-1

Anti-Inflam.

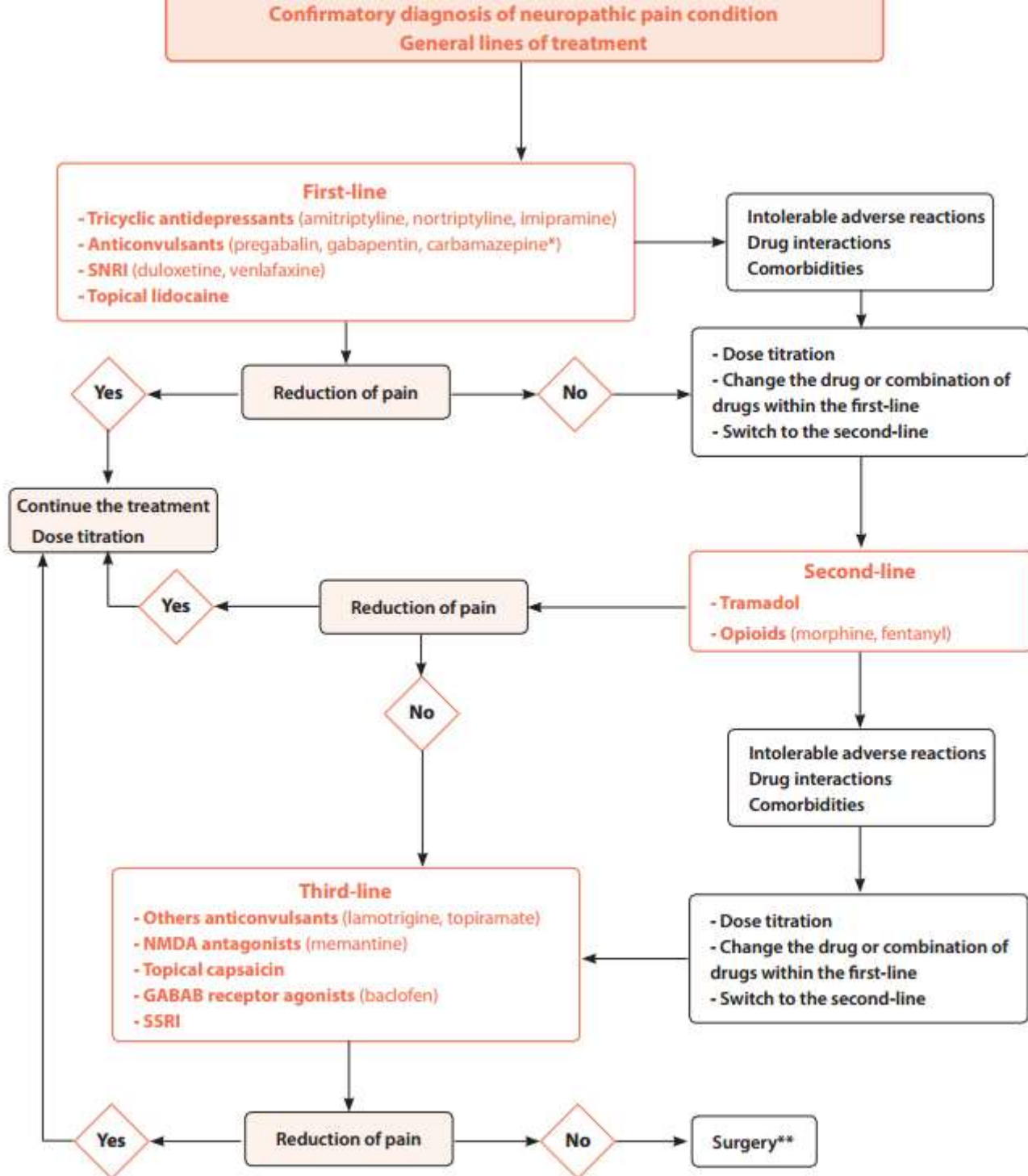
- **Peripherally**
- inhibition of COX enzymes
- Antioxidant effect



DRUG FOR NEUROPATHIC PAIN

Nyeri Neuropatik

- Merup nyeri kronik yang sulit diobati
- nyeri yang berasal dari lesi atau penyakit yang mengenai sistem saraf somatosensoris
- Yg tms nyeri neuropatik a.l :
 - radikulopati servikal dan lumbal,
 - Neuropati diabetik,
 - *cancer related neuropathy*,
 - neuralgia pasca herpes,
 - *HIV-related painful polyneuropathy*,
 - cedera medula spinalis,
 - *central post stroke pain*,
 - neuralgia trigeminal,
 - *complex regional pain syndrome tipe 2* ,
 - Nyeri *phantom*
 - dan lain-lainnya



Drugs	Therapeutic doses	Time	Common side effects	Special Precautions
First-line drugs				
<i>Tricyclic antidepressants</i>				
Nortriptyline Amitriptyline Imipramine	25 – 150 mg/day	6 – 8 weeks	Sedation, anticholinergic effects (dry mouth, constipation and urinary retention), orthostatic hypotension	Cardiovascular diseases, glaucoma, convulsions, suicide risk. Association with tramadol not recommended
<i>Serotonin and norepinephrine reuptake inhibitors</i>				
Duloxetine	30 – 120 mg/day	4 weeks	Asthenia, fatigue, nausea, vomiting, dry mouth, sedation, drowsiness, tremors	Hepatic impairment, renal insufficiency. Association with tramadol not recommended
Venlafaxine	37.5 – 225 mg/day	4 – 6 weeks		Cardiac diseases. Association with tramadol not recommended
<i>Anticonvulsants</i>				
Gabapentin	100 – 3600 mg/day	3 – 8 weeks	Sedation, drowsiness, dizziness, peripheral edema	Renal insufficiency
Pregabalin	150 – 600 mg/day	4 weeks		
Carbamazepine ¹	100 – 1200 mg/day	4 weeks	Drowsiness, nausea, dizziness, ataxia	Hepatic insufficiency, hematologic changes as aplastic anemia, leukopenia and thrombocytopenia
<i>Topical agents</i>				
Lidocaine	3 plasters/day	3 weeks	Skin rash, erythema, burning sensation, itching	Renal insufficiency, severe hepatic impairment

Drugs	Therapeutic doses	Time	Common side effects	Special Precautions
Second-line drugs				
<i>Opioids</i>				
Fentanyl	25 – 100 µg/h	4 weeks		Abuse, addiction, respiratory depression.
Morphine	15 – 200 mg/day	4 – 6 weeks	Nausea, vomiting, constipation, drowsiness, dizziness	Abuse, suicide risk, withdrawal syndrome
Tramadol	50 – 400 mg/day	4 weeks		Abuse, risk of seizures in epileptic patients. Association to antidepressants increase the risk of serotonin syndrome

Drugs	Therapeutic doses	Time	Common side effects	Special Precautions
Third-line drugs				
<i>Others anticonvulsants</i>				
Lamotrigine	25 – 400 mg/day	4 – 6 weeks	Drowsiness, dizziness, skin rash	Hepatic and renal impairment
Oxcarbazepine	300 – 1800 mg/day	4 weeks	Fatigue, drowsiness, dizziness, hyponatremia	Cardiac and renal insufficiency, hypersensibility
<i>Others antidepressants</i>				
Citalopram	10 – 40 mg/day	4 weeks	Nausea, vomiting, drowsiness, dizziness, agitation, tremors	Combination with MAOI, convulsions, suicide, glaucoma.
Paroxetine		4 weeks		
Bupropion	100 – 400 mg/day	3 weeks	Insomnia, anorexia, agitation, tinnitus, headache	Convulsive disease, hepatic disease
<i>NMDA receptor antagonists</i>				
Memantine	10 – 20 mg/day	4 – 6 weeks	Dizziness, headache, constipation, drowsiness	Risk in epileptic patients
<i>Topical agents</i>				
Capsaicine	0.025%	4-6 weeks	Skin rash, erythema, burning sensation	Skin sensibility
<i>GABA_B receptor agonists</i>				
Baclofen	40 – 80 mg/day	4 weeks	Drowsiness, dizziness, ataxia, sedation	Renal insufficiency, epilepsy, nerve diseases, peptic ulcer

Rekomendasi

Trigeminal Neuralgia (intense and unilateral pain (such as electric shock), resulting from traumatic consequences, physiological degenerative processes associated with vascular compression or viral infections, tumor lesions, multiple sclerosis, cerebral aneurysm and alveolar involvement after tooth extraction
First : carbamazepine, oxcarbazepine

- Second: lamotrigine, baclofen
- Third : gabapentin, pregabalin, amitriptyline, duloxetine or venlafaxine

Central pain (trauma, multiple sclerosis, stroke, infeksi, tumor, degenerasi)

- First : Amitriptyline or nortriptyline, pregabalin or gabapentin
- Second / third : lamotrigine, tramadol or opioids such as morphine or fentanyl

• **Postherpetic neuralgia** (common consequence of herpes zoster, whose factors that reactivate the latent virus are unknown.

- First : tricyclic antidepressants such as amitriptyline or nortriptyline, pregabalin, gabapentin and/or topical lidocaine (plaster to 5%)
- Second: opioids such as morphine or fentanyl or topical capsaicin 0,025%
- Third : baclofen or tramadol.

• **Diabetic polyneuropati**

- First : Amitriptyline or nortriptyline, pregabalin or gabapentin
- Second : venlafaxin., tramadol, opioid (Morfin)
- Third : carbamazepine, lamotrigine,



ANALGETIK ADJUVANT

Adjuvant analgesics or co-analgesics

Adjuvant analgesics, which are also referred to as co-analgesics, are medicines that are not primarily used for analgesia. These are medicines that are administered alone or with NSAIDs and opioids that may:

- Enhance the analgesic activity of the NSAIDs or opioids
- Have independent analgesic activity for certain pain types (such as neuropathic pain)
- May counteract the side effects of NSAIDs or opioids

Table 9: Selective Adjuvant Coanalgesics for Pain

Drug Class	Indications	Examples of Drugs + Starting Dose Range	Adverse Effects
Tricyclic antidepressants (po)	Neuropathic pain (burning quality) Added benefit for insomnia or depression	Amitriptyline 10–25 mg qhs Nortriptyline 10–25 mg qhs Desipramine 10–25 mg qhs	Anticholinergic effects. Most prominent with amitriptyline.
Anticonvulsants (po)	Neuropathic pain (sharp, shooting, electric shock-like quality)	Clonazepam 0.5–1 mg qhs, bid or tid Gabapentin 100 mg tid Pregabalin 75 mg bid	Sedation, dizziness, lower extremity edema (elderly and frail more at risk)
Corticosteroids (po, IV, SC)	Card compression, bone pain, neuropathic pain, visceral pain, pain crisis	Dexamethasone 2–20 mg/d Give up to 100 mg IV for pain crisis Prednisone 15–30 mg tid or qid	“Steroid psychosis” delirium, dyspepsia
Local anesthetics (po, IV, SC infusion, transdermal)	Neuropathic pain	Mexiletine 150 mg tid Lidocaine 1–5 mg/kg hourly Lidocaine patch 5%, 12 h on, 12 h off	Lightheadedness, tremor, paresthesias, arrhythmias
N-methyl-D-aspartate (NMDA) receptor antagonists (IV, SC, po)	Neuropathic pain	Ketamine 0.1–0.2 mg/kg/h 5 mg po	Confusion, frightening dreams
Alpha-2 adrenergic agonists (po, ED, transdermal)	Refractory pain. Can be used in combination with an opioid ED	Clonidine	
Bisphosphonates (IV)	Osteolytic bone pain	Pamidronate 60–90 mg over 2 h q2–4wk	Pain flare
Antispasmodic (po, IV)	Muscle spasms	Baclofen 10 mg (po) qd or qid	Muscle weakness, cognitive changes
Botox (SC)	Dystonia, muscle spasms		
Calcitonin (SC, nasal)	Neuropathic pain, bone pain	25 IU/d	Hypersensitivity reaction, nausea

ED = epidural; IV = intravenous; po = by mouth; SC = subcutaneous.

This table should be used as a guide only and not to replace a more in-depth review. Individual dosing depends on each patient's particular situation and comprehensive assessment.

Adapted from References 2, 3, 34, and 37 and based on clinical experience of the author and a variety of published sources.



OBAT ANESTESI LOKAL

OBAT LOKAL ANESTESI

- **Obat Lokal Anestesi** ----> obat yg menyebabkan blokade konduksi impuls di sepanjang jalur saraf pusat maupun perifer secara reversibel setelah anestesi regional
- Dibedakan 2 golongan :
 1. **Amida** (Bupivacaine, Nupercaine, Etidocaine, Lidocaine, Mepivacaine, Prilocaine, Ropivacaine)
 2. **Ester** (Chloroprocaine, Cocaine, Procaine, Tetracaine)

Mekanisme kerja obat anestesi lokal

- Obat lokal anestesi mencegah proses depolarisasi membran saraf dengan **memblok aliran ion Na** → hambatan transmisi impuls saraf (blokade konduksi)
- Kualitas hambatan transmisi impuls nyeri terjadi setelah pemberian, sangat tergantung pada :
 - ✓ karakteristik obat yaitu potensi (ditentukan oleh kelarutan dalam lemak); onset (ditentukan oleh pKa) dan durasi (ditentukan oleh ikatan protein), volume konsentrasi yang dipakai
 - ✓ **penambahan vasokonstriktor (epinephrin)** : memperlambat penyerapan dan memperpanjang efek durasi anestesi 60%.
 - ✓ Cara dan lokasi penyuntikan

CARA DAN LOKASI PENYUNTIKAN

- **Infiltrasi anestesi :**

- ✓ Penyuntikan lokal anestesi ke lokasi yg akan dianestesi.

- **Blok anestesi:**

- ✓ Menyuntikkan lokal anestesi di sekitar saraf utama yg jaraknya jauh dari lokasi yg akan dianestesi.

Kriteria ideal obat anestesi lokal

1. Onset cepat
2. Durasi panjang
3. Dapat dititrasi
4. Toksisitas rendah
5. Tempat kerja terlokalisir
6. Khusus menghambat nyeri,
tidak berefek pada fungsi motorik
7. Dosis relatif kecil
8. Efek samping minimal
9. Reversibel

LIDOKAIN

Mekanisme Kerja :

cegah transmisi impuls saraf atau blokade konduksi → melambatkan lintasan ion sodium melalui kanal Na di membran saraf

Farmakokinetik :

- Absorpsi & distribusi dipengaruhi → tempat injeksi, dosis, epinephrine dan sifat farmakologi.
- Faktor terkait : usia, status kardiovaskuler dan fungsi hepar.
- Eliminasi → metabolisme hepar



ANESTESI UMUM

GENERAL ANAESTHETICS

THE FIRST **GENERAL ANAESTHETICS**

- Nitrous oxide, 1880, Laughing gas
- **Ether**, 1846, explosive
- Chloroform, 1847, Toxic to the liver

THEORIES OF ANAESTHETIC ACTION

- **LIPID THEORY**– Anaesthetics dissolve in lipid part of cell membranes and depress membrane activity
- **PROTEIN THEORY**– Anaesthetics bind to hydrophobic protein site in membranes and depress activity
- Depression of transmitter release rather than nerve conduction. **Not via receptors**
- *We don't really know how they*

FOUR STAGES OF ANAESTHESIA

1. Analgesia

2. Delirium

- loss of consciousness,
- delirious excitement
- reflex activity

3. Surgical anaesthesia

- deep unconsciousness,
- respiratory depression
- muscle relaxation

4. Medullary paralysis

- respiratory & cardiovascular, depression, death

ADVERSE EFFECTS

- Respiratory & cardiac depression
- Sensitisation of heart to catecholamines
- Malignant hyperthermia
- Aspiration of gastric contents – use endotracheal tube
- Hepatotoxicity
- Renal toxicity

MONITORING THERAPI : PAIN RATING SCALES



0
NO HURT



2
HURTS
LITTLE BIT



4
HURTS
LITTLE MORE



6
HURTS
EVEN MORE



8
HURTS
WHOLE LOT



10
HURTS
WORST

Mild

Moderate

Severe

Pain threshold

Pain tolerance

CHOOSING PAIN KILLER AND ITS COMBINATIONS

10 Pain Intensity Scale

0	1	2	3	4	5	6	7	8	9	10
Mild				Moderate			Severe			

	paracetamol or/+ NSAID ± adjuvant analgesic	NSAID ± weak opioid ± adjuvant analgesic	Strong opioid ± NSAID ± adjuvant analgesic
--	--	---	---

Pemilihan Analgetik

- ① Efficacy (indication)
- ① Safety (side effect)
 - **Not only** GI toxicity
 - Cardiovascular toxicity
 - Renal toxicity
 - Bleeding
 - Bone healing impairment etc
- ① Suitability (contra-indication)
- ① Availability
- ① Pharmacokinetics and drug interaction
- ① Daily cost
- ① Evidence based medicine

TERIMA KASIH

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