APPLICATIONS OF NSAIDS IN MUSCULOSKELETAL DISORDERS

DR SHAMS SULEMAN

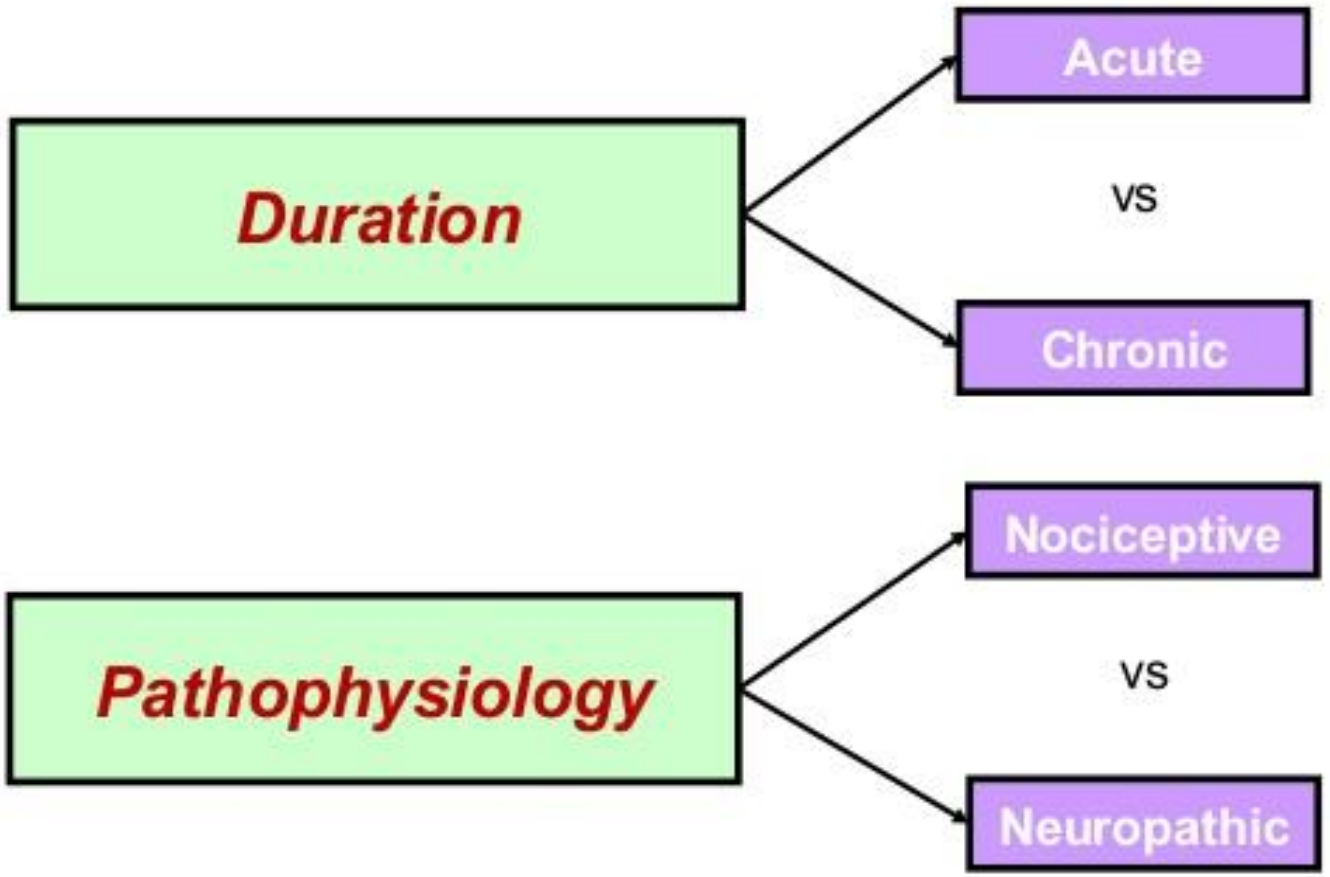
LEARNING OBJECTIVES

- Discuss the role of NSAIDs in the treatment of various musculoskeletal disorders
- Describe the salient features of various NSAIDs used for these indications

Disorders of Muscle Tissue

- Muscle tissues experience few disorders
  - Heart muscle is the exception // MI, CAD
  - Skeletal muscle – remarkably resistant to infection
  - Smooth muscle – problems stem from external irritants

Classification of Pain



Acute Pain vs Chronic Pain

Acute

- Usually accompanied by obvious tissue damage
- Increased autonomic nervous activity
- Pain resolves with healing of the underlying injury
- Serves a protective function

vs.

Chronic

- Pain that extends 3 or 6 months beyond onset or beyond the expected period of healing[1]
- Ceases to serve a protective function[2]
- Degrades health and functional capability[2]
- Depressed mood[3]

[1] Turk and Okifuji. *Bonica's Management of Pain*. 2001.
[2] Chapman and Stillman. *Pain and Touch*. 1996.
[3] Fields. *NNBN*. 1991;4:83-92.

Classification of Pain

Nociceptive

- *Pain that arises from a stimulus that is outside of the nervous system – receptors stimulated*
- *Proportionate to the stimulation of the receptor*
- *When acute serves a protective function*
- *Musculoskeletal disorders are a very common cause of nociceptive pain*

vs

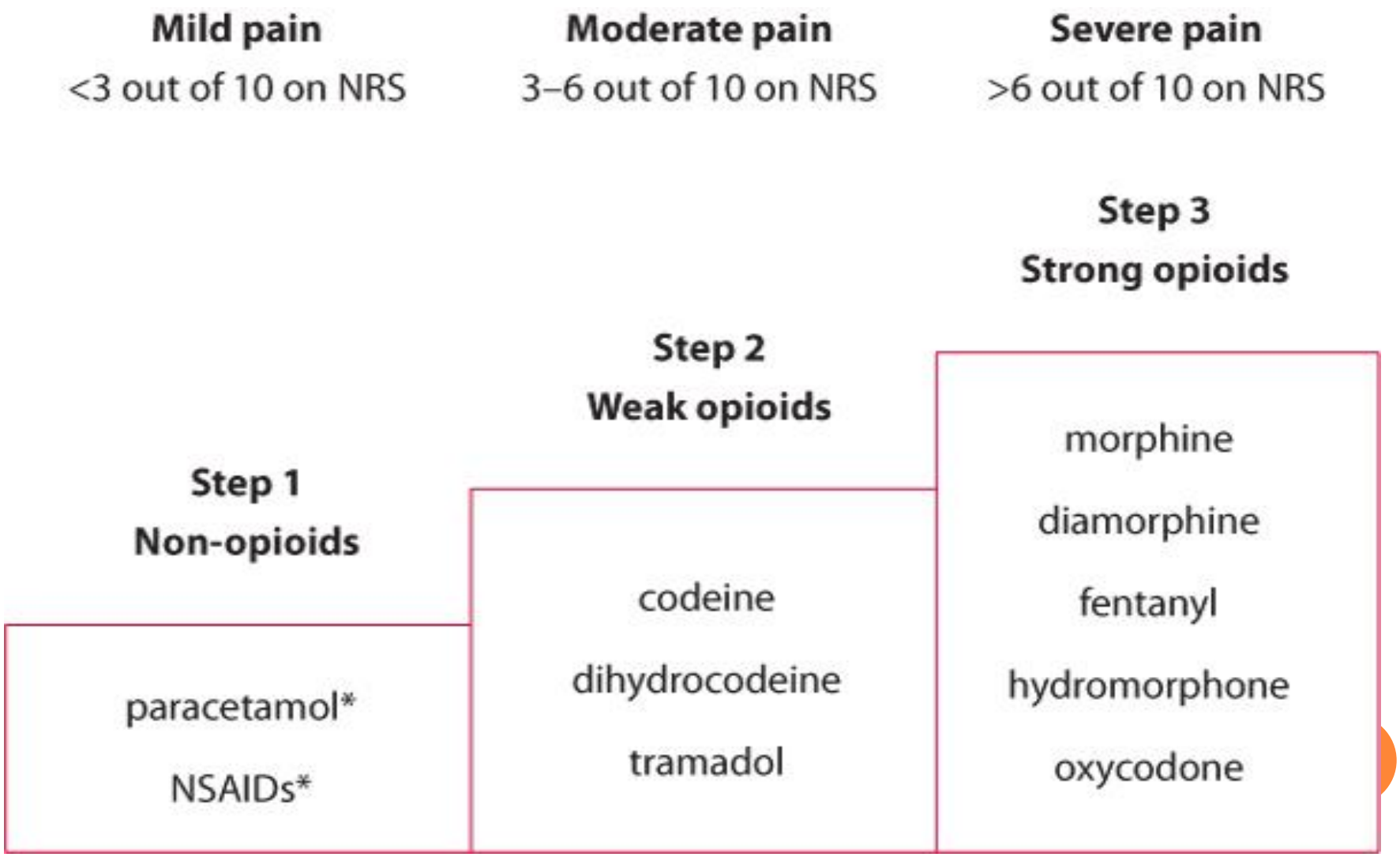
Neuropathic

- *Pain initiated or caused by a primary lesion or dysfunction in the nervous system*
- *No nociceptive stimulation required*
- *Disproportionate to the stimulation of receptor*

Recommendations for pain medications

- Paracetamol: first line drug, safe
- NSAIDs : unresponsive to paracetamol.
- COX-2 inhibitors or NSAIDs + PPI in GI risk
- Topical agents (NSAIDs, capsaicin): safe and effective in mild pain
- Opiod: patients contraindicated for NSAIDs or COX-2, or ineffective or poorly tolerated
- Anticonvulsant (Gapapentin, Pregabalin) benefit in neuropathic pain

W H O ANALGESIC LADDER



ARTHRITIS

TYPES

- Osteoarthritis
- Rheumatoid arthritis

OSTEOARTHRITIS

OSTEOARTHRITIS

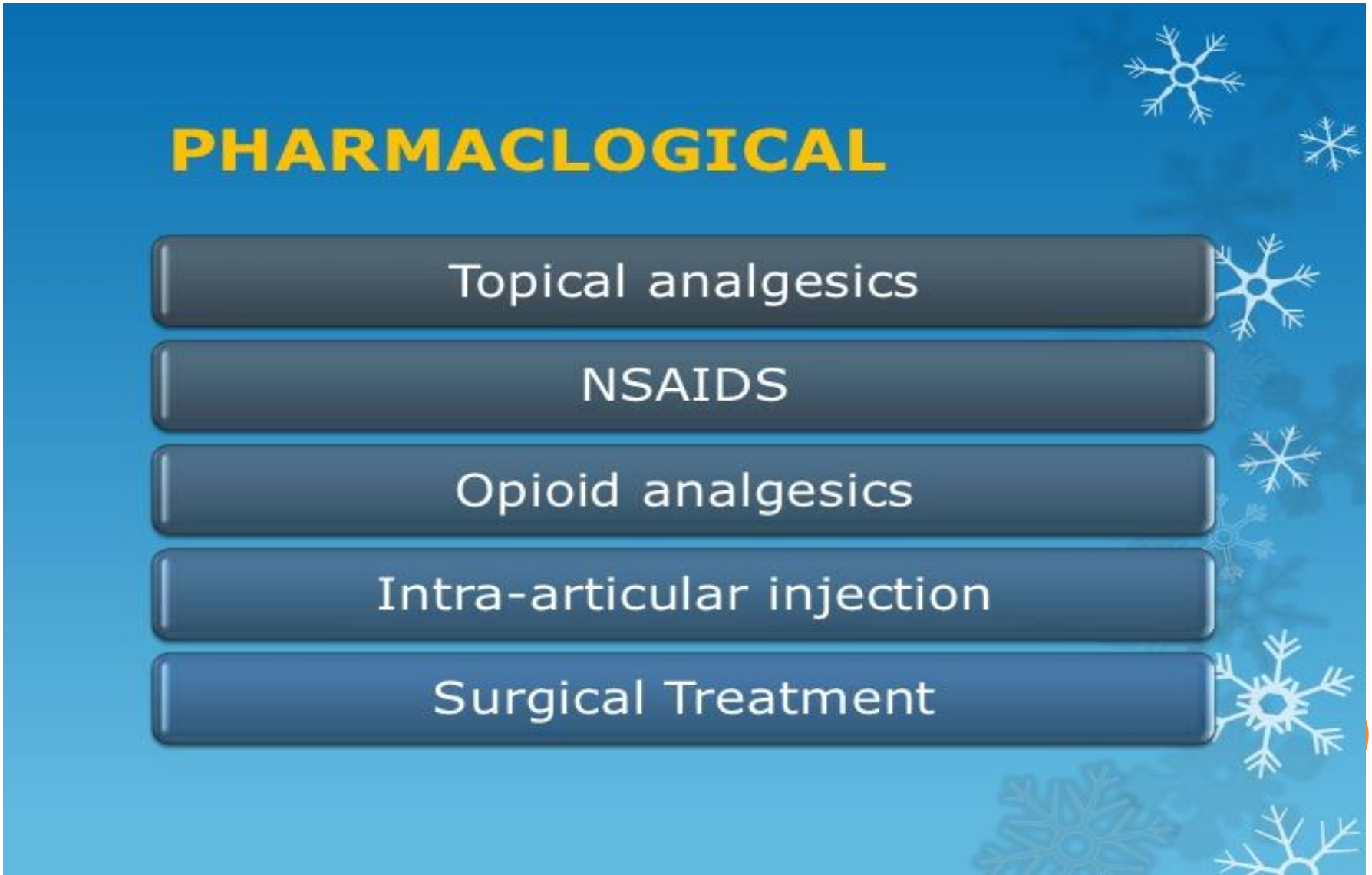
ETIOLOGY

- **Secondary osteoarthritis**
- Trauma
- Mechanical stress
- Inflammation
- Joint instability
- Neurologic disorders
- Skeletal deformities
- Hematologic disorders
- drugs

MANAGEMENT

- Rest and joint protection
- Heat and cold applications
- Nutritional therapy and exercise
- Complementary and alternative therapies
- Drug therapy
  - ✓ Acetaminophen
  - ✓ NSAIDS
  - ✓ Antibiotics
  - ✓ Intra articular injection of corticosteroids
  - ✓ Intra articular hyaluronic acid

OSTEOARTHRITIS



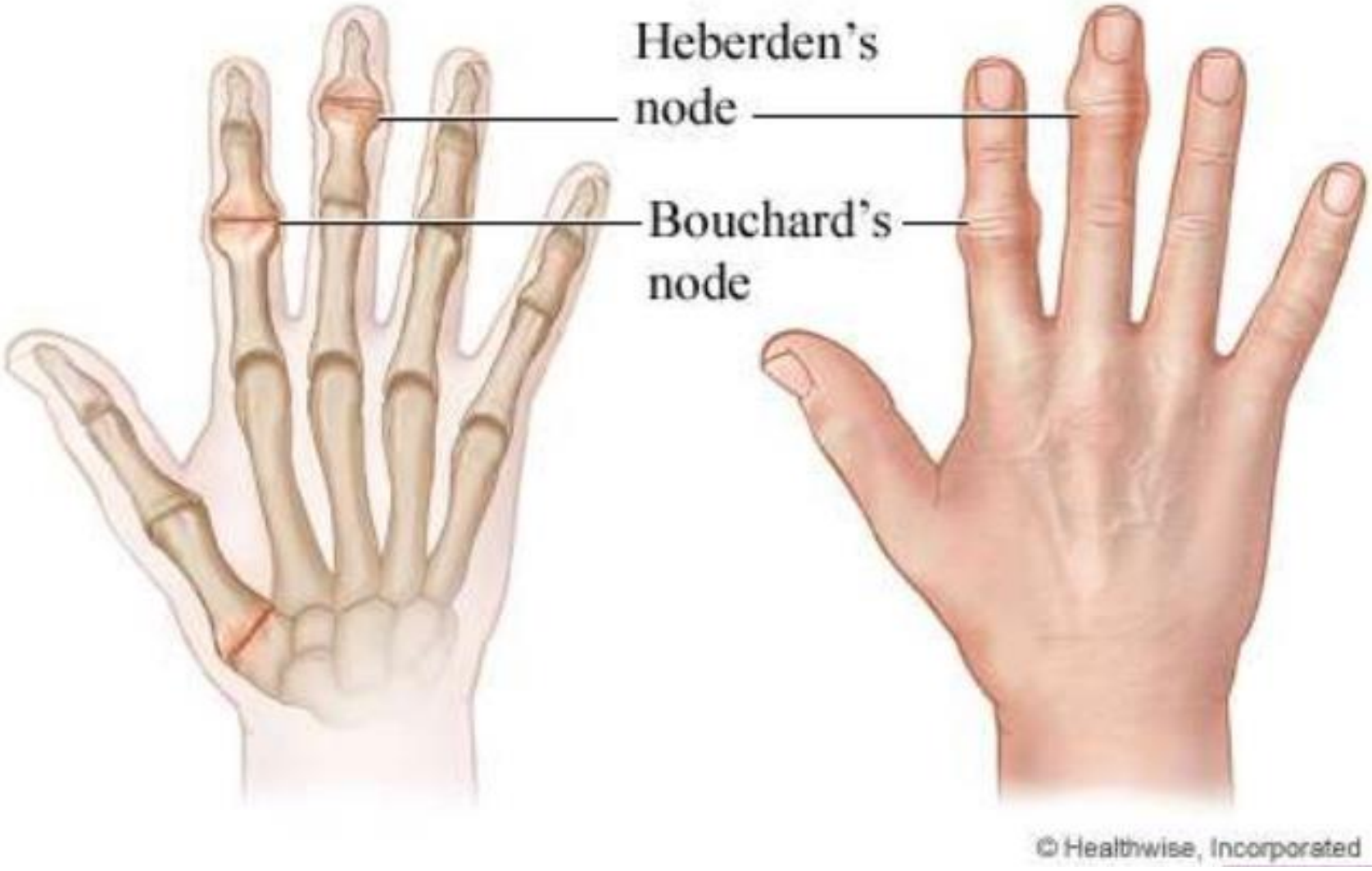
RHEUMATOID ARTHRITIS

MANAGEMENT

Drug therapy

- Disease modifying anti rheumatic drugs
  - Hydroxychloroquine.
  - Leflunomide.
  - Methotrexate
- Biologic | targeted therapy
- Antibiotics
- Immunosuppressants
- NSAIDS and salicylates

RA vs OA



MUSCULOSKELETAL SYSTEM

Contusions, Strains and Sprains

MANAGEMENT

Emergency care	rest, ice, compression, and elevation for the first 24 to 48 hours
Diagnosis	x-ray, magnetic resonance imaging (MRI)
Medications	nonsteroidal anti-inflammatory drugs (NSAIDs)
Treatment	immobilized with a cast or splint surgery to repair the torn ligaments, muscle, or tendons physical therapy for rehabilitation

MUSCULOSKELETAL SYSTEM

Joint Trauma

	ROTATOR CUFF INJURIES	KNEE INJURIES	JOINT DISLOCATION
Manifestations	shoulder pain, limited ROM	immediate pain, a tearing or popping sensation, swelling	pain, deformity, and limited motion of the affected joint
Diagnosis	history and physical assessment x-ray and MRI		
Treatment	RICE NSAIDs physical therapy surgery	RICE NSAIDs physical therapy surgery	RICE, NSAIDs close reduction manual traction surgery

MUSCULOSKELETAL SYSTEM

Repetitive Use Injuries

	CARPAL TUNNEL SYNDROME	BURSITIS	EPICONDYLITIS
Emergency Management	RICE in the first 24 to 48 hours		
Medications	NSAIDs narcotics corticosteroids	NSAIDs narcotics	NSAIDs narcotics corticosteroids
Treatment		Surgery	

NSAIDS

Classification

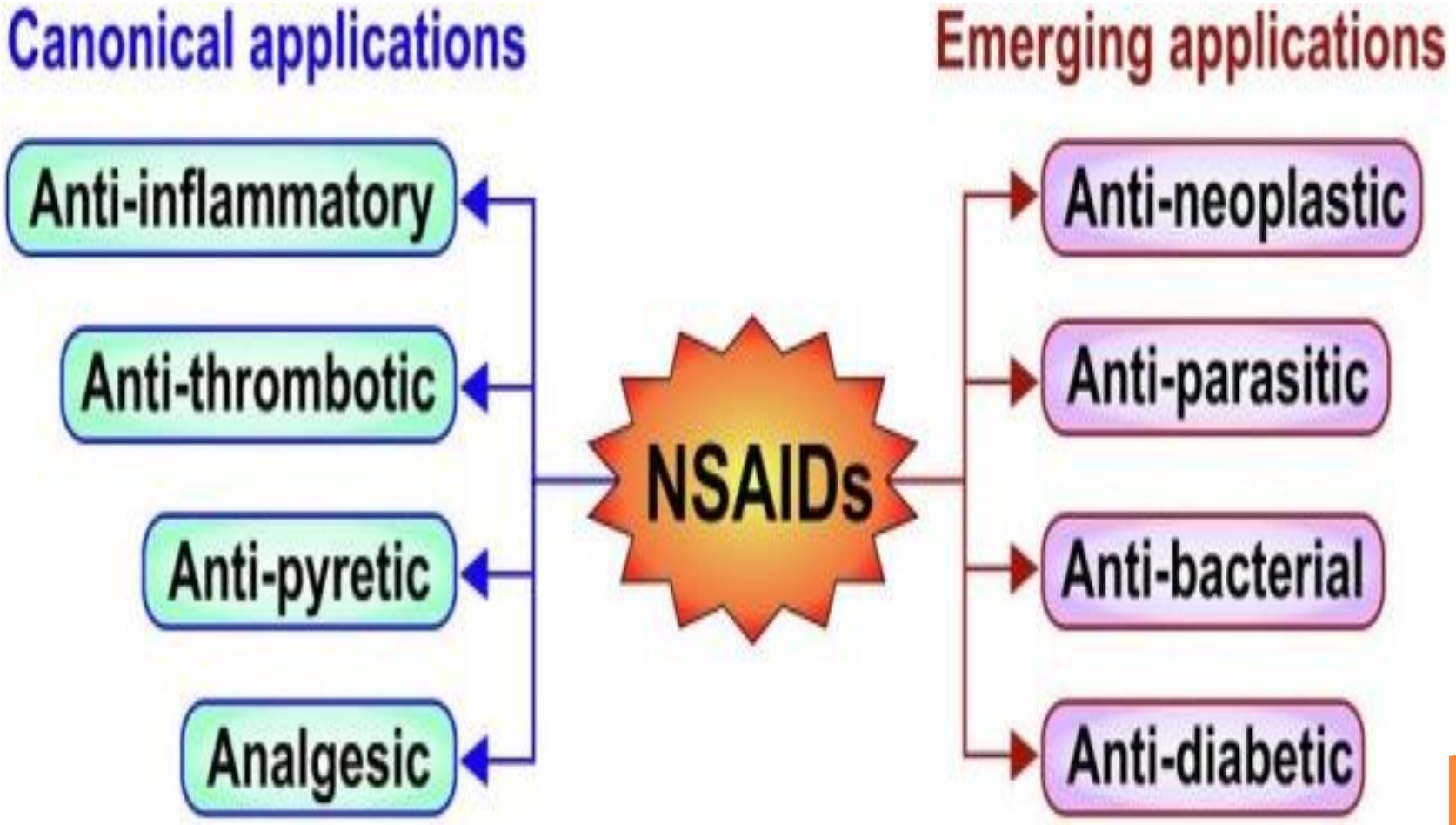
Traditional – Nonselective COX inhibitors	
Group	**Drugs**
Salicylic acids	Aspirin
Propionic acids	Naproxen, Ibuprofen, Ketoprofen, Oxaprozin and Flurbiprofen
Anthranilic acid	Mefenamic acid
Aryl-acetic acid derivative	Diclofenac and Aceclofenac
Oxicam derivatives	Piroxicam and Tenoxicam
Pyrrolo-pyrrole derivative	Ketorolac, Indomethacin, Nabumetone
Indole derivatives	Sulindac and Indomethacin
Pyrazolone derivative	Phenylbutazone, Oxyphenbutazone

NSAIDS

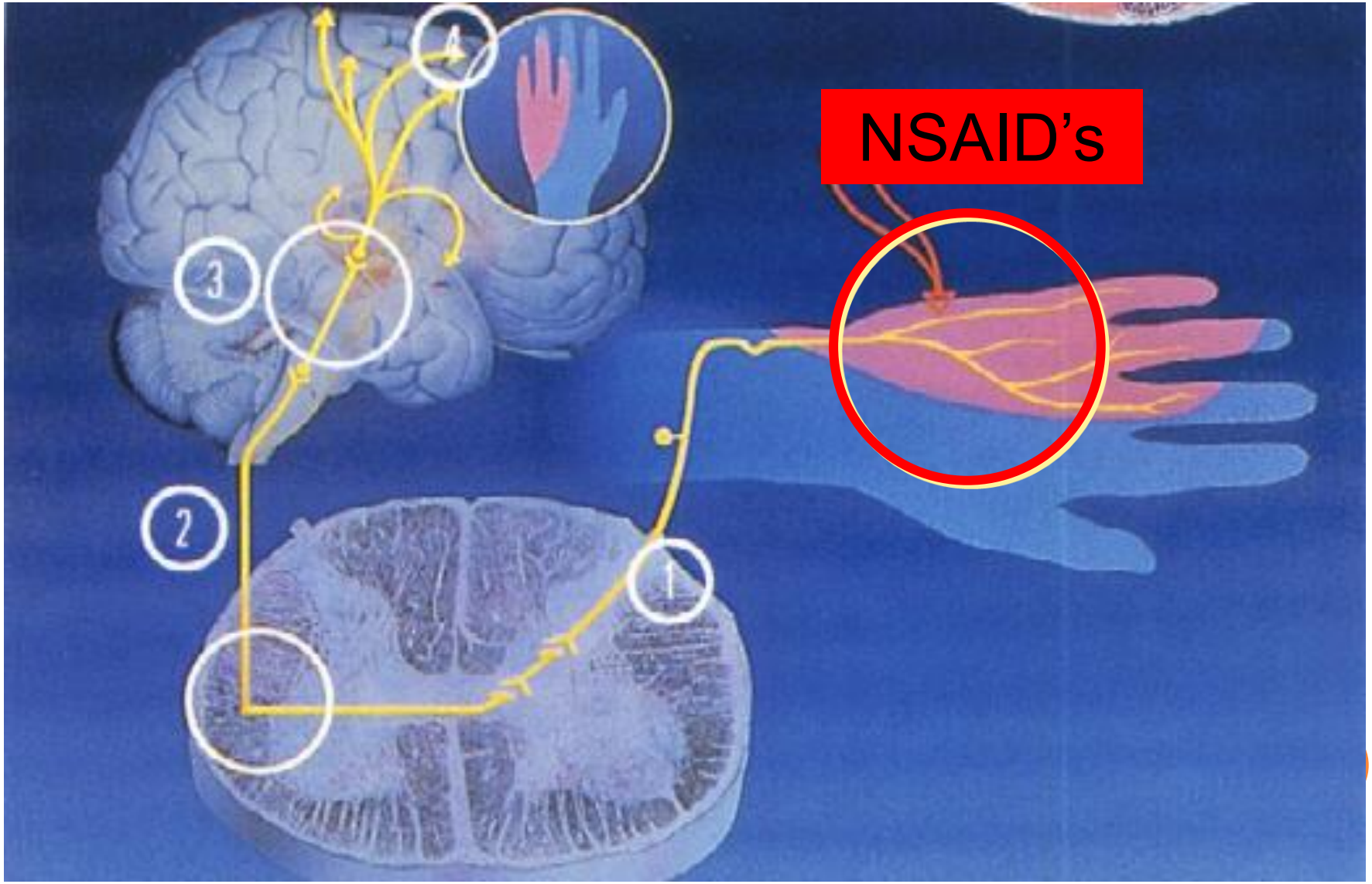
Classification – contd.

Preferential COX-2 inhibitors	Nimesulide, Diclofenac, Aceclofenac, Meloxicam and Nabumetone
Selective COX-2 inhibitors	Celecoxib, Etoricoxib and Parecoxib
Analgesic-antipyretic with poor antiinflammatory action:	
Paraaminophenol derivative	Paracetamol (acetaminophen)
Pyrazolone derivative	Metamizole and Propiphenazone
Benzoxazocine derivative	Nefopam

NSAIDS


Canonical applications
Anti-inflammatory
Anti-thrombotic
Anti-pyretic
Analgesic
NSAIDs
Emerging applications
Anti-neoplastic
Anti-parasitic
Anti-bacterial
Anti-diabetic

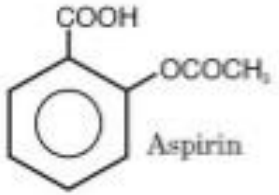
SITE OF ACTION



NSAIDs induced Analgesia

- **Peripheral component:**
  - PGs (especially E_2 and I_2) sensitize afferent nerve endings to pain – induces chemical and mechanical stimuli
  - Induce hyperalgesia – by affecting transducing property of free nerve endings – normal stimuli may become painful
  - NSAIDs do not block direct PG application related pain and tenderness
  - But, block the pain sensitizing mechanism induced by – Bradykinin, TNF and Interleukins (IL) and others – by inhibiting COX-2
  - More effective against pain due to inflammation
- **Central Component:** Antihyperalgesic (analgesic) effects through inhibition of PGs release in spinal dorsal horn and CNS

Salicylates



- **ASPIRIN** is acetylsalicylic acid, the Prototype - converted in the Body to Salicylic acid – Oldest analgesic
- Other important salicylates – Sulfasalazine, Diflunisal
- Natural Sources - fruits, vegetables, herbs, spices, nuts, and tea

Aspirin - Uses

- **Analgesic :** Backache, myalgia, toothache, joint pain, pulled muscle and dysmenorrhoea
- **Antipyretic :** Fever of any origin – Paracetamol safer
- **Acute Rheumatic fever:** 75 – 100 mg/kg/day (or, 4 – 5 gm/day) – marked symptomatic relief – all cases
  - dose reduced after 4 - 7 days and maintained for 2 - 3 weeks till s/s stops - withdrawal should be gradual
- **Rheumatoid Arthritis:** Reduction in pain, swelling and stiffness – large dose
- **Osteoarthritis:** As and when needed – Paracetamol is the choice
- **Post-myocardial infarction** and **post stroke:** Routinely used – inhibits platelet aggregation (TXA_2) at low dose (60 – 100mg/day) – but, high dose can reverse (PGI_2 inhibition)
  - New onset or sudden onset angina (risk of infarction) - 75 to 150 mg/day for 12 weeks …. Also in TIA
- **Other uses:** PIH, PDA, Familial colonic polyposis and Prevention of colonic cancer

THERAPEUTICS USES OF ASPIRIN

ANALGESIA

- Most frequently used analgesic
- For mild to moderate pain
- Severe pain is not controlled by aspirin

a. Used alone in pain like:

- Headache, myalgia, arthralgia, neuralgia, osteomyelitis, osteoarthritis, toothache, dysmenorrhea

b. With opioids – synergistic action

- In pain of cancer metastases in bone
- Post operative pain- ↓ requirement of opioids

ANTI-INFLAMMATORY

(in large doses)

- Rheumatoid arthritis
- Acute rheumatic fever along ē benzyl penicillin

ANTI-PYRETIC

- Lowers fever

ANTI-PLATELET

(in low doses 75 – 100mg/day)

- For transient ischemic attacks cerebrovascular stroke
- Prophylaxis of unstable angina, MI
- Thrombosis after coronary artery by pass grafting

URICOSURIC AGENT

(large doses >4 gm /d)

CLOSURE OF PDA

LOWERS INCIDENCE OF COLON CANCER

Niacin- flushing

Systemic mastocycosis

ADVERSE EFFECTS OF ASPIRIN

1. **Gastric upsets:**

- Erosive gastritis & Gastric ulceration
  - Hematemesis
  - Melena
  - Occult Blood In stool

- Dyspepsia and heart burn
- Nausea & vomiting

2) Effects on CNS

Salicylism:

- (In large doses): Tinnitus, deafness, dimness of vision, dizziness, ataxia, mental confusion, vertigo, nausea & vomiting, sweating, thirst
- (In Toxic Doses): Hyperpyrexia, CV collapse, convulsions, ketosis, coma

3) Related to Kidney:

Analgesic Nephropathy

4) **Reye syndrome**

4. **Respiratory system**

- Hyperventilation
- Compensated respiratory alkalosis (high doses)
- Uncompensated acidosis (toxic doses)

5. **Blood**

- Hypo prothrombinaemia
- Increase bleeding tendency

6. **Allergic / Hypersensitivity Reactions**

- Bronchospasm
- Urticaria
- Rhinitis
- Hay Fever

Aspirin – Drug Interactions

- **Aspirin and Probenecid:**
  - Antagonize Uricosuric action of **probenecid**
  - Probenecid become ineffective in **Gout**
- **Aspirin and oral anticoagulants** (**warfarin** and **sulfonylureas**)
  - Toxicity (increased tendency of bleeding)
- **Aspirin and anti-hypertensive:**
  - NSAIDs cause fluid retention and oedema – antihypertensive effects are decreased
- **Aspirin and Diuretics:** (**furosemide** and **thiazides**)
  - Blunting of Furosemide effects

Aspirin – Contraindications

1. Sensitive Persons
2. Children with viral diseases
3. Peptic ulcer disease and bleeding disorders
4. Chronic liver diseases
5. Diabetes, CHF and juvenile Rh. Arthritis
6. G-6-PD deficient persons
7. **Stop** prior to surgery, near term pregnancy, breast feeding mothers etc

NAPROXEN

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

- **MECHANISM OF ACTION**

NAPROXEN IS APPROXIMATELY 20 TIMES POTENT AN INHIBITOR OF COX AS ASPIRIN. AN ADDITIONAL PROPERTY IS INHIBITION OF LEUKOCYTE MIGRATION, WITH A POTENCY SIMILAR TO COLCHICINE.

ADVERSE EFFECTS

NAPROXEN CAUSES ALL OF THE ADVERSE EFFECTS COMMON TO NSAIDS.

NON-SELE
DICLOFENAC SODIUM
TIVE COX INHIBITORS

- Phenylacetic acid derivative
- Combinations are available (+ misoprostol)
- 150 mg/d impair renal blood flow & GFR
- GI ulceration less frequent
- Elevation of serum aminotransferases

Preparations: eye drops, topical gel, suppository

Dose: 50-75mg qid

IBUPROFEN

- Phenylpropionic acid derivative
- Anti inflammatory effect start at 2400 mg/dl (equivalent to 4gm aspirin anti-inflammatory effect)
- Lower dose has analgesic effect
- Closure of patent ductus arteriosus in preterm infants
- Less decrease in urine output, less fluid retention
- Decreases antiplatelet effect of aspirin
- Oral I/V, topical

INDOMETHACIN

- Indole derivative
- Potent non-selective COX inhibitor and may also inhibit Phospholipase A and C
- Reduce neutrophil migration and decrease T-cell and B-cell proliferation
- Effective in joint pain, swelling & tenderness
- Gout, arthritis
- Accelerate closure of patent ductus arteriosus
- Pancreatitis, frontal headache
- $t_{1/2}$ prolonged by probenecid

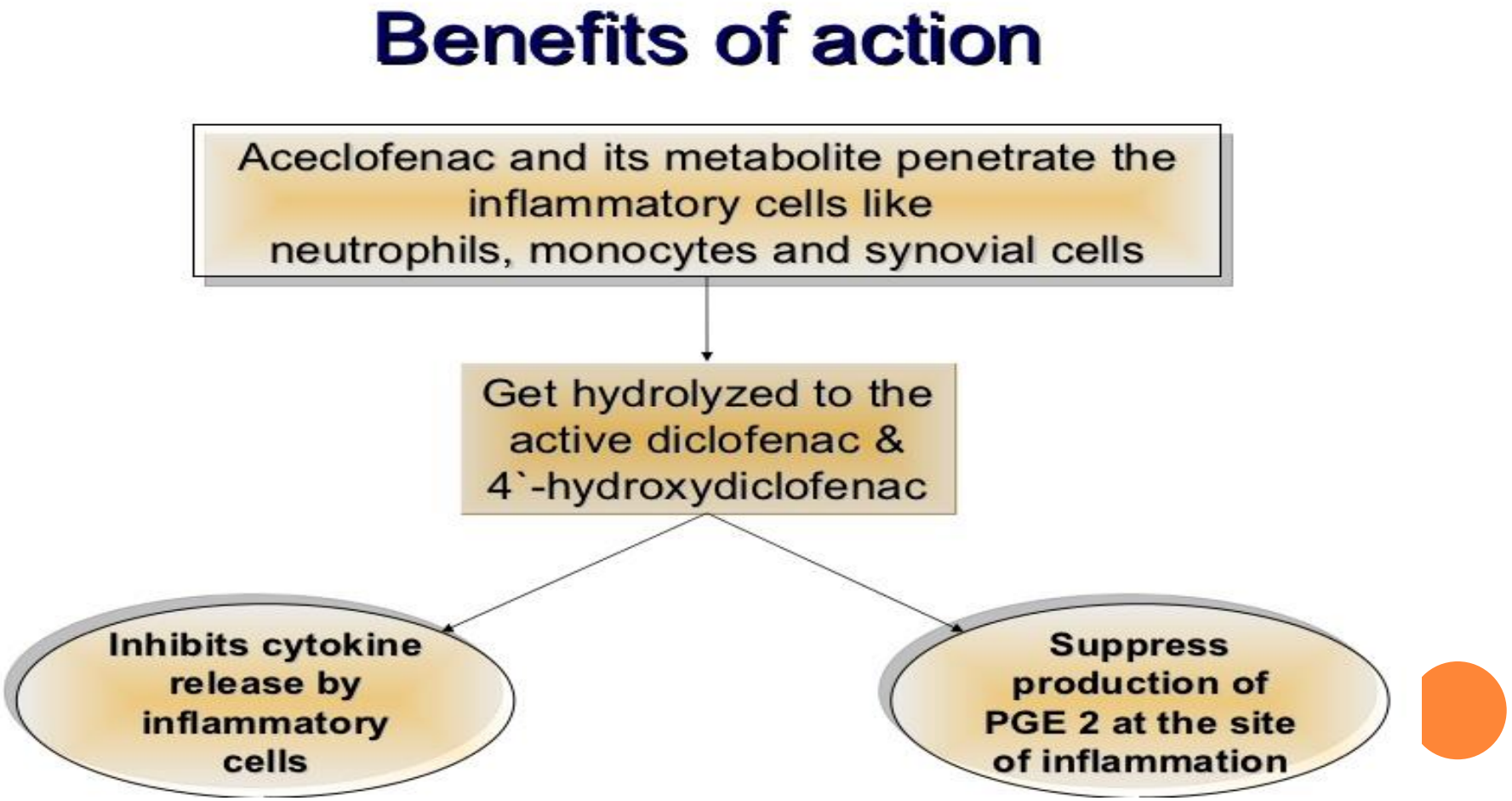
Acetic acid - Indomethacin

- Indole acetic acid derivative - Potent anti-inflammatory and prompt antipyretic
  - Relieves only inflammatory and injury related pain
  - Highly potent inhibitor of PG and neutrophil motility
- **Use:** Reserve drug - ankylosing spondylitis, destructive arthropathies, psoriatic arthritis, postoperative pain, malignancy associated fever, medical closure of PDA
- **Kinetics:** well absorbed orally, 90% PP bound and $t_{1/2}$ 2 – 5 Hours
- **ADRs:** High incidence of gastric and CNS side effects (COX-1 related) – gastric, irritation, nausea, anorexia, bleeding and diarrhoea
  - **CNS:** Frontal headache, dizziness, ataxia, mental confusion, hallucination, depression and psychosis
  - Leucopenia, hypersensitivity, rash etc.
  - Increased risk of bleeding – low platelet aggregation
- **Contraindications:** machinery operators, drivers, psychiatric & epileptic patients kidney disease, pregnancy & children

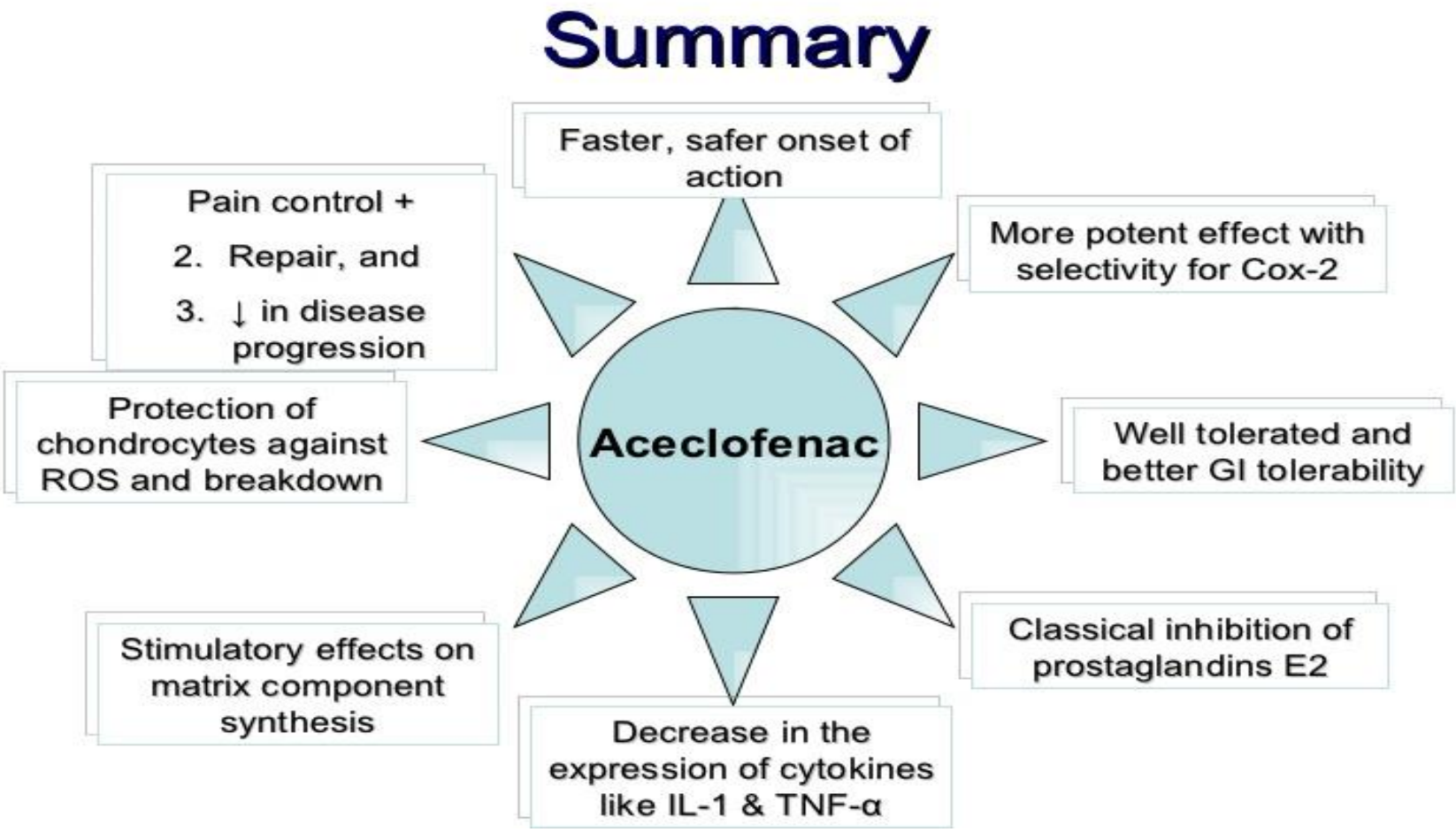
Acetic acid derivatives - Ketorolac

- Potent analgesic – but modest anti-inflammatory – post operative pain – equal efficacy with Morphine (but no receptor interaction)
- Inhibits PG synthesis – inhibits pain peripherally
- **Uses: Given IM and orally -** Post-operative, dental, musculo-skeletal pain – also in renal colic, migraine – short term management of moderate pain – rated superior to aspirin and paracetamol and equivalent to ibuprofen
  - Concurrent use with morphine (reduce dose) – but not used with anticoagulant – not to be used for more than 5 days
- **Kinetics:** Well absorbed orally and IM – highly plasma protein bound; $t_{1/2}$ 5 – 7 Hrs – 60% excretes unchanged in urine
- **ADRs:** Nausea, abdominal pain, dyspepsia, ulceration, dizziness, nervousness, pain in injection site, rise in serum transaminase, fluid retention etc.

ACELOFENAC


Benefits of action
Aceclofenac and its metabolite penetrate the inflammatory cells like neutrophils, monocytes and synovial cells
Get hydrolyzed to the active diclofenac & 4`-hydroxydiclofenac
Inhibits cytokine release by inflammatory cells
Suppress production of PGE 2 at the site of inflammation

ACELOFENAC


Summary
Faster, safer onset of action
More potent effect with selectivity for Cox-2
Well tolerated and better GI tolerability
Classical inhibition of prostaglandins E2
Decrease in the expression of cytokines like IL-1 & TNF-α
Stimulatory effects on matrix component synthesis
Protection of chondrocytes against ROS and breakdown
Pain control +
2. Repair, and
3. ↓ in disease progression
Aceclofenac

Topical NSAIDS

- NSAIDS are also effective topically – gel/spray etc.
- **Advantages:**
  1. Attains higher conc. Locally in muscles and joints – low blood levels
  2. GI and other systemic ADRs are minimized
  3. First pass metabolism avoided
- **Kinetics:** slow absorption – 10 times longer time to attain peak plasma conc. to oral dosing
  - Highest blood level – 15% of the same oral dose,
  - Local conc. Upto 4 - 6mm high (dermis); 25 mm in muscles (low)
  - Overall efficacy depends on site
- **Uses:** Osteoarthritis, sprains, sports injuries, spondylitis and soft tissue rheumatism etc. – safety no issue but efficacy (!) local application, massaging – counter irritant - menthol and methyl salicylate
  - More efficacious in short lasting musculo-skeletal pain

COX-2 SELECTIVE INHIBITORS

- Celecoxib
- Rofecoxib
- Valdecoxib
- Parecoxib
- Etoricoxib
- Lumaricixib

- Inhibit prostaglandin synthesis by the COX-2 isozyme
- Analgesic, antipyretic and anti inflammatory effects
- No effect on platelet aggregation
- No cardio protective effect

CELECOXIB

- Highly selective COX- 2 inhibitor.
- Half life is 11 hrs
- Metabolized mainly in the liver
- Effective in rheumatoid arthritis and osteoarthritis.
- Less production of peptic ulcer
- Inhibit COX 2 mediated prostacyclin synthesis in vascular endothelium- platelet aggregation

ACETAMINOPHEN

- Active metabolite of phenacetin
- Weak COX-I and COX-2 inhibitor
- Inhibits COX-3 centrally
- No significant anti-inflammatory effects

Pharmacokinetics:

- Peak blood level is reached in 30-60 min
- Metabolized by hepatic microsomal enzymes and form acetaminophen sulphate and glucronide
- N-acetyl-*p*-benzo-quinoneimine (NAPQI)---- Toxic to liver and kidneys

ACETAMINOPHEN

- 325 – 1000mg (total dose not > 4000mg)
- Headache, myalgia, postpartum pain
- In rheumatoid arthritis with anti-inflammatory agent
- Preferred to aspirin in peptic ulcer, in children with viral infections, haemophilia, bronchospasm

Paracetamol Uses

- Most commonly used – over the counter drug
- Headache, mild migraine, musculoskeletal pain dysmenorrhoea etc.
- 1st choice in osteoarthritis, not effective in Rheumatoid arthritis
- Safest Antipyretic in children – no Reye`s syndrome
- **Advantages** – 1) lesser gastric irritation, ulceration and bleeding (can be given in ulceration) 2) does not prolong bleeding time 3) Hypersensitivity rarely 4) no metabolic disturbances 5) can be given in all age group – pregnancy-lactation 6) No significant drug interactions

Classification of Corticosteroids (CS)

Drug	ROA	Duration of action	Mineralo-C potency	Gluco-C potency
Short-acting drugs				
Hydrocortisone (cortisol)	Oral, parenteral, topical	8-12 hr	1	1
Cortisone	Oral, parenteral, topical	8-12 hr	0.8	0.8
Fludrocortisone	Oral	8-12 hr	200	10
Intermediate-acting drugs				
Methyl-prednisolone	Oral, parenteral, topical	12-36 hr	0.5	5
Prednisolone	Oral	12-36 hr	0.7	3.5
Triamcinolone	Oral, parenteral, topical	12-36 hr	0	5
Long-acting drugs				
Betamethasone	Oral, parenteral, topical	24-72 hr	0	30
Dexamethasone	Oral, parenteral, topical	24-72 hr	0	30

Common therapeutic uses of glucocorticoids

- **Respiratory disease**
- Asthma,COPD,sarcoidosis,hayfever,prevention and treatment of ARDS.

- **Cardiac disease**
- Post-myocardial infarction syndrome

- **Renal**
- Some nephrotic syndromes, some glomerulonephritides

- **GI disease**
- Ulcerative colitis
- Crohn's disease
- Autoimmune hepatitis

- **Rheumatological disease**
- SLE,polymyalgia rheumatica, cranial arteritis,juvenile idiopathic arthritis, vasculitides,rheumatoid arthritis

- **Neurological disease**
- Cerebral oedema

- **Skin disease**
- Pemphigus,eczema

- **Tumours**
- Hodgkin's lymphoma, other lymphomas

- **Transplantation**
- Immunosuppression

- **THE MOST COMMON INDICATION FOR STEROID USE IS AS AN ANTI-INFLAMMATORY DRUG**

CENTRALLY ACTING MUSCLE RELAXANTS

(SPASMOLYTICS)

- Benzodiazepines; Diazepam
- GABA derivatives; Baclofen, Gabapentin
- Central α2 agonists; Tizanidine
- Mephenesin derivatives

  Mephenenisine

  Carisoprodol

Muscle relaxant

- Indication

  -Muscle spasm, Reduction

- Precaution

  -Constipation

  -Water retention

  -Specific action of each muscle relaxants : Atropine like effect (orphenadine), peripheral Vasodilatation (tolperisone)

Choices of NSAIDS

1. Mild to moderate pain – Paracetamol or low dose Ibuprofen
2. Post operative acute short lasting pain – Ketorolac, Propionic acid derivatives, diclofenac or nimesulide
3. Acute musculo-skeletal, osteoarthritic or injury pain – Paracetamol or propionic acid
4. Exacerbation of Rh. Arthritis, acute gout, ankylosing spondylosis – naproxen, piroxicam, indomethacin
5. Gastric intolarance to NSAIDS - Selective COX-2 inhibitors
6. H/o asthma – nimesulide or selective COX-2 inhibitors
7. Hypertension or risk of heart attack – COX-2 inhibitors and PA derivatives
8. Paediatric – paracetamol, elderly – low dose of NSAIDS
9. Pregnancy – Paracetamol
10. Fast acting ones – fever, headache and other short lasting pain SR preparations for chronic long lasting pain
11. IHD, hypertension, DM – consider drug interactions

Choices of NSAIDS ???

- H/o asthma
  - Selective COX-2 inhibitors
- Hypertension or risk of heart attack
  - COX-2 inhibitors
- Paediatrics
  - Paracetamol, elderly – low dose of NSAIDS
- Pregnancy
  - Paracetamol

Combinations

- Aspirin + Paracetamol – Supra-additive
- Also Paracetamol + Ibuprofen and
- Diclofenac + Paracetamol

REFERENCES

- **Basic & Clinical Pharmacology, 14th Edition**

  Bertram G. Katzung

- **Katzung & Trevor's Pharmacology: Examination & Board Review, 12th Edition**

- **Lippincott illustrated review Pharmacology: 6th Edition**

Email address for queries on the topic

drshams11@hotmail.com