THE UNIVERSITY OF WESTERN AUSTRALIA

DENT 3005:Introduction to Pharmacology

Immunomodulators & anti-inflammatory

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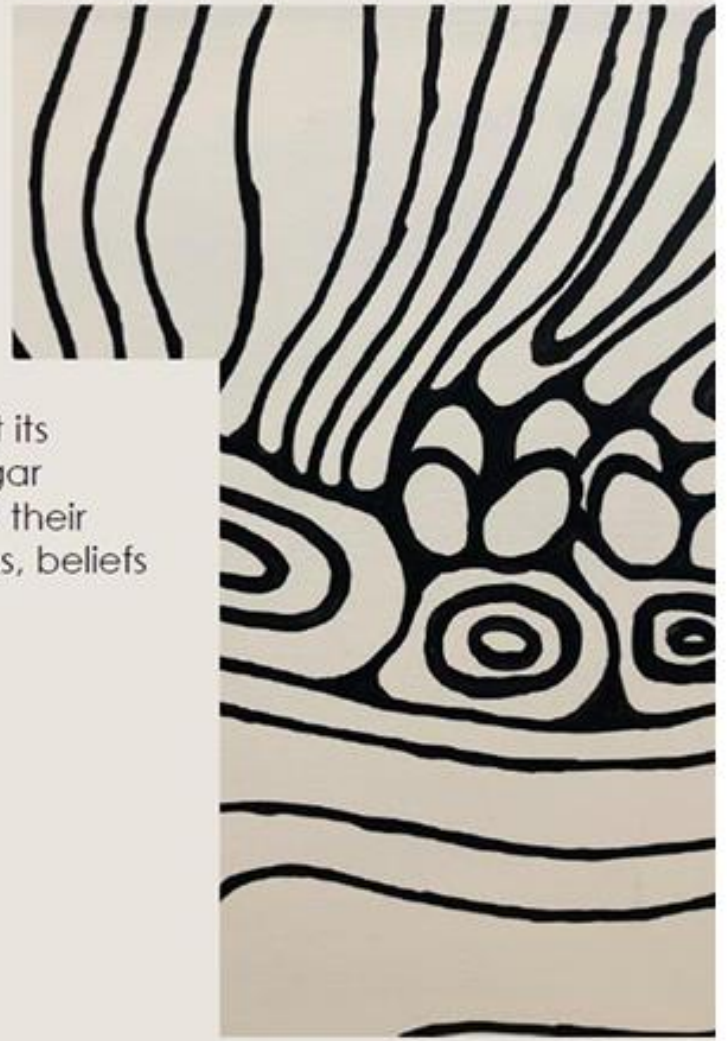
Acknowledgement of country

The University of Western Australia acknowledges that its campus is situated on Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practise their values, languages, beliefs and knowledge.



Artist: Dr Richard Barry Walley OAM

Learning Outcomes

Learning objectives

1) Understand the different types of immunomodulators and anti-inflammatory drugs
2) Broad understanding of RA, OA and gout and the pharmacological agents used in these conditions
3) Recognise oral and dental side effects of these drugs
4) Understand drugs interactions with dental medications
5) Applied knowledge to clinical scenarios

Immunomodulators

- **Stimulate or suppress immune system**
  - Tx autoimmune & inflammatory diseases: RA, psoriasis, UC, Crohn's, SLE, organ transplantation
- **Rheumatoid arthritis (RA):** autoimmune disease attacking healthy tissue in joints
  - **Tx rationale:** provide sx relief, maintain level of function, and prevent damage to bones, joints, and other organs
- **Osteoarthritis (OA):** deterioration of cartilage at the ends of bones in the joints
  - **Tx rationale:** Relieve symptoms (pain and stiffness) and improve joint function to enable the patient to exercise and increase strength and mobility

Rheumatoid Arthritis

- **What is it?**
  - Autoimmune disease, inflammatory disorder
  - Chronic & progressive
  - Systemic, significant morbidity and mortality
- **Pathophysiology**
  - Lymphocyte mediated inflammatory disease
  - Stimulating antigens → abnormal inflammatory response
  - Inflammatory mediators (cytokines)TNF-α, IL-1, IL-6
  - Synovial membrane hypertrophies → synovial pannus
  - Cytokine rich synovial fluid → damage to adjacent supporting structures

Rheumatoid Arthritis: treatment

- **Non-pharmacological**
  - Exercise, diet, footcare, massage, heat/cold packs etc
- **Pharmacological**
  - **Analgesics:** paracetamol, NSAIDs, opioids
    - Manage symptoms but do not alter course of disease
  - **Corticosteroids:** not first line, short duration of tx due to adverse effects
    - Anti-inflammatory, immunosuppressant and disease modifying effects
  - **DMARDs:** biologicals and non biologicals
    - DMARDS: aka conventional antirheumatic drugs
    - Biological DMARDS: TNF alpha antagonists and cytokine modulators

(DMARDs) Conventional antirheumatic drugs

Generic name (brand name)	Drug class	Selected ADR	Drug interactions (dentally related)
Azathioprine (Azapin, Imuran)	Purine antimetabolite	Dose-related myelosuppression, infection, GI irritation, mouth ulceration	Nil
Ciclosporin (Neoral)	Calcineurin inhibitors	Gingival hyperplasia, opportunistic infections	Increases toxicity risks of calcineurin inH: Azole antifungals, clarithromycin, erythromycins, NSAIDs
Hydroxychloroquine (Plaquenil)	Anti-inflammatory and immunosuppressive Antimalarial	Retinal damage, rash, GI irritation	Drugs that prolong QT interval: clarithromycin, erythromycin, fluconazole
Leflunomide (Arava, Ataris)	Pyrimidine synthesis inhibitor	(common) pharyngitis, dyspnea (infrequent) oral candidiasis, stomatitis, taste disturbance	Hepatotoxic, adhere strict dosage for paracetamol to prevent increase risk of hepatotoxicity
Methotrexate (Methoblastin)	Antimetabolite	Myelosuppression, mucosal ulcers, GI irritation, infections	Hepatotoxic May increase risks of MTX toxicity: NSAIDs, penicillins, nitrous oxide
Sulfasalazine (Salazopyrin, Pyralin)	5-aminosalicylate	Myelosuppression, rash (infrequent) yellowing of skin	Nil
Auranofin (Ridaura)	Gold Salt	Dyspepsia, stomatitis, mouth ulcers, dry mucous membranes, gingivitis	Nil

Calcineurin inhibitors

- **MOA:** form complexes with cytoplasmic immunophilins
  - Block the action of calcineurin in activated T cells
  - Prevents production of interleukin-2 and other cytokines
- **Ciclosporin:** gingival hyperplasia [common in children & adolescent]
- **Tacrolimus:** gingival hyperplasia a [rare ADR]
- **Drug interactions: increases toxicity risks of calcineurin inH**
  - Azole antifungals
  - Clarithromycin & erythromycins
  - NSAIDs

Generic name	Brand Name
Ciclosporin	Neoral
Tacrolimus	Prograf

Corticosteroids

- ***Recap:*** *we have discussed a few in respiratory & adrenal insufficiency*
- **MOA:** regulate gene expressions (glucocorticoid & mineralocorticoid effects)
- **ADR:** remember *steroids adverse reactions* slide
- **Drug interactions**
  - (Methylprednisolone, dexamethasone) + azole: increase steroid adverse effects
  - Aspirin: decrease salicylate concentration
  - NSAIDs: increase risk of gastric ulceration

Generic name	Brand Name
Betamethasone	Celestone inj
Cortisone	Cortate
Dexamethasone	Dexmethsone
Hydrocortisone	Solu-Cortef Inj
Methylprednisolone	Solu-Medrol inj
Prednisolone	Predsolone…
Triamcinolone	Kenacort-A inj

Corticosteroids ADRs

- Infection
- Delayed wound healing
- Steroid rosacea
- Perioral dermatitis
- Skin atrophy
- Bruising
- Acne
- Facial flushing
- Pupura
- Depigmentation
- Telangiecstasia
- Steroid induced crushing's

Janus Kinase (JAK) inhibitors

- **MOA:** inh Janus kinase (JAK) → suppress immune response
- **ADR:** infections (serious and opportunistic)
- **Drug interaction**
  - **Azoles, clarithromycin, erythromycin:** increase toxicity risk of tofacitinib & upadacitinib

Generic name	Brand Name
Baricitinib	Olumiant inj
Tofacitinib	Xeljanz inj
Upadacitinib	Rinvoq inj

(bDMARDs) TNF alpha antagonists

- **MOA:** Bind to TNF alpha and inhibit its activity.
  ADR: [common >1%]
  - Infections (opportunistic or serious)
  - Mouth ulcers, sore that do not heal, pain or excessive bleeding of gums
- **Drug interactions:** not dentally related drugs (phew)
  - Not to be used with other bDMARDs

Generic name	Brand Name
Adalimumab	Humira inj
Certolizumab	Cimzia inj
Etanercept	Enbrel inj
Golimumab	Simponi inj
Infliximab	Remsima inj

(bDMARDs) Cytokine modulators

- **Abatacept:** binds to CD80 and CD86 on antigen-presenting cells
  - Prevent full activation of CD28 T lymphocytes → reducing cytokine production and inflammation
- **Anakinra:** neutralises the activity of IL-1
- **Rituximab:** reduce T cell activation and resulting cytokine production
- **Tocilizumab:** inhibits the activity of IL-6
- **Drug interactions:** not dentally related drugs (phew)
  - Not to be used with other bDMARDs

Generic name	Brand Name
Abatacept	Orencia inj
Anakinra	Kineret inj
Rituximab	Riximyo inj
Tocilizumab	Actemra inj

Selected ADR
Dizziness
Infections (opportunistic or serious)
Mouth ulcers
Vertigo

Additionall reading: for fun!

- **Not to be assessed ☺**
  - Systemic Lupus Erythematosus (SLE)
  - Spondyloarthropathies (seronegative arthritis)
  - Ankylosing spondylitis
  - Psoriatic arthritis
  - Juvenile arthritis
  - Fibromyalgia
  - Infectious arthritis (chronic and acute)
  - Osteomyelitis
  - Raynaud’s syndrome

Rheumatoid arthritis drugs

Dental implications

- **DMARDs:** dose related myelosuppression
  - Patient at risks of infections
  - Check slide 6 for selected ADR
- **Calcineurin inhibitors**
  - Ciclosporin: gingival hyperplasia in youth
  - Check slide 8 for selected ADR
- **Corticosteroids:** interactions and ADRs
- **ADRs relating to dental**
  - JAK inh (slide 11)
  - Gold Salt (slide 7)
  - bDMARDs: TNF alpha antagonists & cytokine modulators (slide 12, 13)

Osteo-arthritis

- **What is it?**
  - Gradual breakdown of cartilage, the smooth, protective tissue that covers the ends of bones in joints
  - Commonly affects joints in your hands, knees, hips and spine
- **Pathophysiology**
  - “wear and tear”
  - Breakdown of cartilage, destruction of articular cartilage
  - Remodelling of bone
  - Loss of joint space → bone rub on bone

Osteo-arthritis: treatment

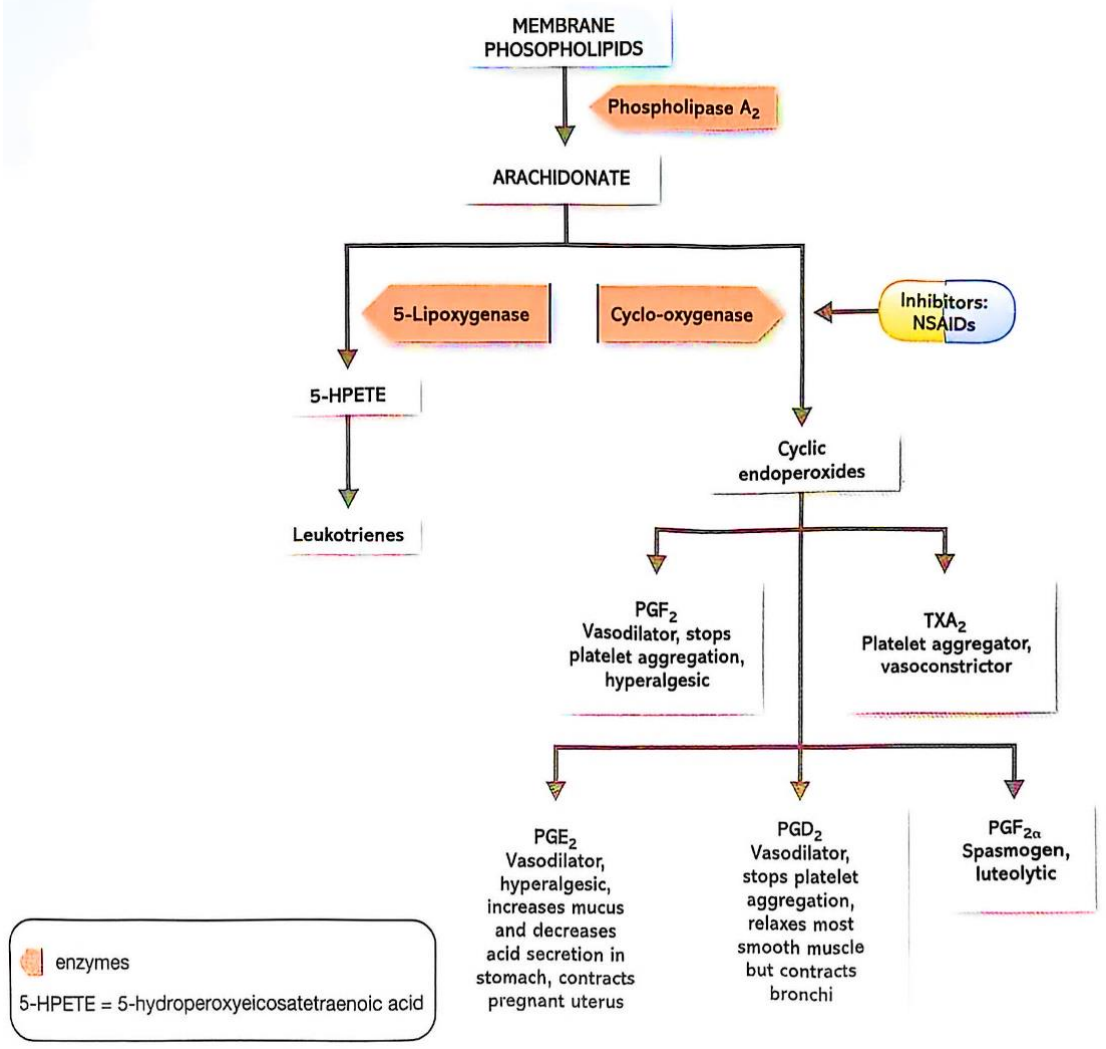
- **Non-pharmacological**
  - Exercise, diet, footcare, massage, heat/cold packs etc
- **Pharmacological**
  - Supplements
  - Paracetamol: preferred drug cf to NSAIDs
  - NSAIDs
    - Topical can be use but costly
    - Oral: aim for the lowest effective dose for the shortest duration
  - Opioids
  - Intra-articular corticosteroids
    - Short-term relief of pain for moderate-to-severe flare of symptoms
    - Adjunct to oral therapy

Rheumatoid arthritis Vs Osteo-arthritis

Features	Rheumatoid arthritis	Osteoarthritis
Affected joints	Smaller, multiple, proximal finger, bilateral	Large, often one, distal finger, unilateral
Age of onset	30-50	Typically older population
Inflammation	Yes	Maybe
Other associated sx	Systemic illness involving other organs	None
Blood tests	Usually elevated ESR, CRP, RF and anti-CCP	Usually none
Pharmacological treatment	NSAIDs, DMARDs, bDMARDs, corticosteroids	Paracetamol, maybe NSAIDs & opioids

Prostaglandin & COX enzymes

- **Prostaglandin**
  - Synthesized from AA
  - Present at site of inflammation
  - Augment action of histamine, vasodilation, increase vascular permeability
- **Cyclooxygenase enzymes**
  - Convert AA→ prostaglandin & TxA2
  - COX 1: constitutive
    - Homeostasis
    - Regulate renal blood flow
    - Platelet aggregation
    - Stomach mucous production
    - Regulate stomach acid secretion
  - COX 2: inducible
    - Inflammation



NSAIDs

Nonselective NSAIDs (COX1&2-Inh)	
Generic name	**Brand Name**
Aspirin	Solprin
Diclofenac	Voltaren
Ibuprofen	Nurofen
Indomethacin	Arthrexin, Indocid
Ketorolac	Toradol
Mefenamic Acid	Inza, Naprosyn
Naproxen	Feldene-D, Mobilis
Piroxicam	

Selective NSAIDs (COX2-Inh)	
Generic name	**Brand Name**
Celecoxib	Celebrex
Etoricoxib	Arcoxia
Meloxicam	Melobic, Mobic
Parecoxib	Dynastat inj

Precautions

- Existing renal impairment
  - Worsen renal function
- Existing platelet disorder
  - Affect coagulation → ↑ bleeding risks
- Existing cardiac disease
  - Na and H2O retention → HTN, peripheral oedema, worsening HF
- Existing GI conditions
  - Ulceration & ↑ bleeding risks
- Existing asthma: ↑ bronchospasm

Interactions (MANY)

- Anticoagulants
  - E.g. warfarin, clopidogrel
- Renally excreted drugs
  - E.g. lithium, ACE inhibitors, digoxin
- K+ sparing drugs
  - E.g. ACE inhibitors, “sartans”, spironolactone
- Antihypertensives
- Bisphosphonates
  - E.g. alendronate
- Corticosteroids
- “Triple whammy”
  - NSAID + diuretic + ACE/ARB

NSAIDs ADR

- **Serious ADR**
  - Vomiting blood or material that looks like coffee grounds
  - Bleeding from your back passage (rectum), black sticky motions or bloody diarrhoea
  - Swelling of the face, lips or tongue which may make swallowing or breathing difficult
  - Asthma, wheezing, shortness of breath
  - Sudden or severe itching, skin rash, hives
  - Pain or tightness in the chest
- **Dental related**
  - Sore mouth/tongue
  - Aphthous ulcers
  - Lichenoid drug eruptions
  - Drug induced pemphigus
  - Prolonged bleeding

NSAIDs Dental implications

Common ADRs

- Gastrointestinal: upset stomach, ulcers, bleeding
- Renal: oedema, hypertension, kidney damage
- Respiratory: bronchospasm, asthma exacerbation
- Cardiovascular: increased risk of heart attack, stroke

Dental ADRs

- Sore mouth/tongue
- Aphthous ulcers
- Lichenoid drug eruptions
- Drug-induced pemphigus
- Prolonged bleeding during procedures

Considerations

- Monitor for bleeding risk (esp. during surgery)
- Check for gastrointestinal and renal issues
- Assess for asthma history
- Be aware of drug interactions with other medications (e.g., anticoagulants)

Drugs for gout

- **What is it?**
  - Progressive inflammatory disease
- **Pathophysiology**
  - Persistent hyperuricaemia: serum urate >0.42mmol/L
  - Formation monosodium urate crystals
- **Treatment rationale**
  - **Acute flare:** provide sx relief
  - **Chronic gout:** lower serum urate
- **Pharmacological**
  - NSAIDs: except aspirin
  - Colchicine
  - Corticosteroids: oral, IM, IV
  - Urate lowering drugs
    - Xanthine oxidase inH
    - Uricosurics

Xanthine oxidase inhibitors

- **Allopurinol & febuxostat**
  - **MOA:** Inhibit xanthine oxidase → reduce production of uric acid
  - **Drug interactions**
    - Allopurinol & Amoxicillin: increase risks of rash
  - **ADR (infrequent)**
    - Allopurinol: altered taste sensation

Generic name	Brand Name
Allopurinol Febuxostat	Allosig, Progout Adenuric

Other drugs for gout

- **Colchicine**
  - **MOA:** inhibits neutrophil migration, chemotaxis, adhesion and phagocytosis in inflamed tissue
  - **Drug interactions**
    - Clarithromycin, erythromycin& azole antifungals: increase colchicine concN
    - NSAIDs: monitor in patients w/ reduced renal function
  - **ADR (common)**
    - Diarrhoea, nausea, abdominal discomfort, vomiting, pharyngo-laryngeal pain

Generic name	Brand Name
Colchicine	Colgout, Lengout

Other drugs for gout

- **Probenecid**
  - **MOA:** Increases renal excretion of uric acid by blocking its renal tubular reabsorption
  - **Drug interactions**
    - Aspirin: reduced uricosuric effect of probenecid
    - Cephalosporins & penicillins: increases half-life and prolongs activity of cephalosporin
    - Indomethacin & ketorolac: increases concN of these drugs
  - **ADR (infrequent)**
    - Sore gums

Generic name	Brand Name
Probenecid	Pro-cid

Drugs for gout Dental implications

- **NSAIDs:** monitor for gastric ulcers and bleeding risks during procedures
- **Colchicine:** monitor for gastrointestinal discomfort and interactions with antibiotics
- **Corticosteroids:** monitor for delayed healing, oral thrush and infection
- **Allopurinol:** altered taste and oral irritation
- **Probenecid:** sore gums may occur, monitor for oral discomfort
- **Drug Interactions:** review interactions, especially with antibiotics and NSAIDs, in patients with renal issues

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