



Musculoskeletal System & Medication

Objectives

01

This presentation will discuss common drugs used in musculoskeletal presentations with an overview of their physiology, how drugs work and mechanism of action.

02

The discussion will focus on use of steroids, analgesia and anti inflammatories.

03

Provide a brief overview of common musculoskeletal disorders seen in primary care.



How Drugs Work

Most drugs act at cellular level, but some act outside cells.

E.g. Bicarb used for acid indigestion. Stomach contains an acid environment, bicarb will chemically neutralize the acid and this occurs in the lumen of the stomach outside cells.

Most drugs work on the proteins in blood, which are cellular and may be at the surface of the cell or inside the cell.

- Most protein targets are receptors.
- Other protein targets are:
- Ion channels – calcium channel blockers for HPT
- Enzymes - L-dopa for Parkinsons
- Transport proteins – inhibit neurotransmitter uptake e.g. Prozac.

Protein Targets

- Receptors have complex three dimensional structures within which pockets are formed.
- These are occupied by a small molecule: neurotransmitters or hormones which are produced by the body or drugs
- Small molecules referred to as ligands
- They bind to specific receptor sites and occupy and activate the receptors

Receptor

- This is when a ligand(natural and drugs)....think dopamine and levodopa....activate the receptor and change the cell in which they are found.
- Adrenal is from the adrenal medulla(think kidneys and medulla)
- Adrenoreceptors are divided into 5, or possibly 6 types: α_1 , α_2 , β_1 , β_2 , β_3 , and potentially β_4 .

Agonists

- The activation of α and β adrenoceptors usually elicits opposing responses:
 - α receptor activation leads to constriction of veins and arterioles.
 - β receptor activation leads to dilation of veins and arterioles

Adrenoreceptors

Adrenoceptor agonists

α_1 -Adrenoceptor agonists



These can be used to treat hypotension through vasoconstriction, leading to increased blood pressure and cardiac arrhythmias through activation of vagal reflexes.



Also valuable adjuncts to local anaesthetics, as vasoconstriction can slow the systemic dispersal of the anaesthetic.



Drugs in this class include phenylephrine and methoxamine.

α_2 -Adrenoceptor agonists

- Despite the tendency of α -adrenoceptor agonists to cause vasoconstriction, these can be used to treat hypertension.
- This unexpected activity occurs through action at the CNS, reducing signal to the heart and so lowering cardiac activity and constriction of the peripheral vasculature.
- Drugs in this class include methyldopa and clonidine.
- Clonidine can also be used in protection against migraine.

Hence, β_1 acts on the heart and β_2 on the lungs.

B-Adrenoceptor agonists:
These can be used to treat hypotension, cardiac arrhythmias and cardiac failure.

- They stimulate the rate and force of cardiac contraction.
- Simultaneously, they lead to a drop in peripheral vascular resistance.
- These combined effects can result in palpitations, sinus tachycardia and serious arrhythmias.
- Drugs in this class include xamoterol and dobutamine

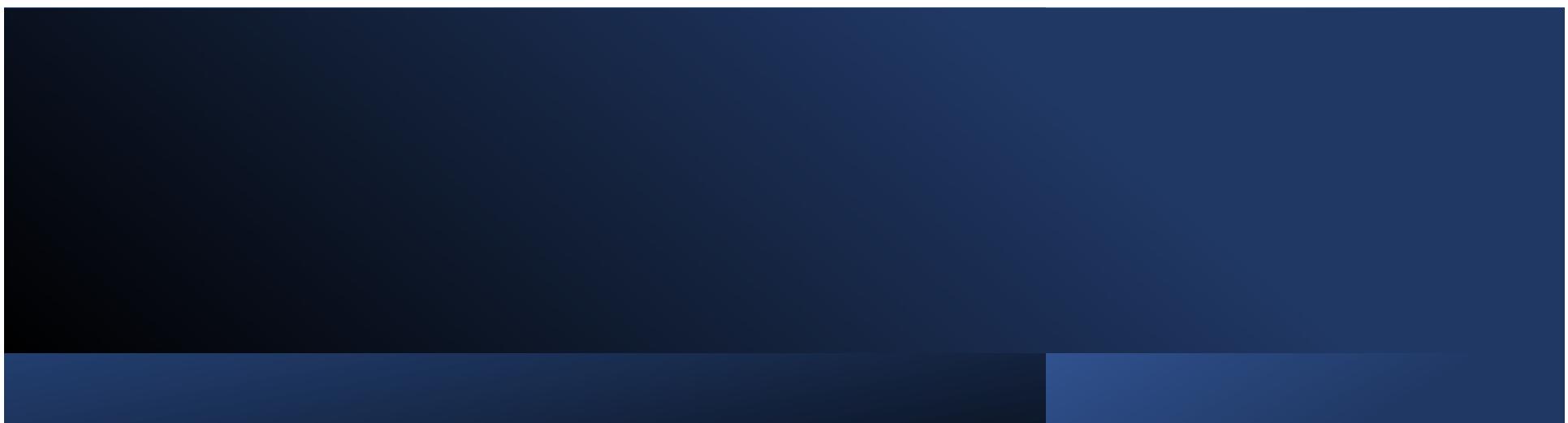
• β_2 -Adrenoceptor agonists lead to muscle relaxation and so find use in treatment of asthma (salbutamol).

Antagonists

- Ligands that bind but do not activate the receptor.
- By occupying receptors, they reduce the binding of the natural agonist
- E.g. antipsychotics which occupy dopamine receptors hence reducing its effect.e.g. in schizophrenia.
- E.g. Atenolol
- What effects does this have on muscles?

- To read more on drug pharmacology
- Boarder,M;Newby,D. and P. Navti (2010)Pharmacology for Pharmacy and the Health Sciences.Oxford University Press: New York.
- ISBN 978-0-19-955982-4

Now that you have a brief overview of drugs, we shall discuss anti inflammatories which are commonly used in treating musculoskeletal disorders



Inflammatory Response

Innate

- Quick response.
- No antigen. No memory
- Increase vascular permeability –swelling
- Attract and activate inflammatory cells
- Release of histamine
- Chemical constituents are prostaglandin, thromboxanes and leukotrienes
- Cellular components are mast cells and neutrophils.
- Sensitization of pain receptors. Heat
- **These responses are protective, allowing the body to repair itself.

Adaptive

- Recognition of antigen
- Production of antibodies
- Develop ‘memory’ for future invasions. Hence, the basis of vaccinations.
- Body produces ‘self’ and ‘non self’ antigens to prevent it attacking its own cells.
- System can break down in e.g. SLE, MS, Coeliac disease

Cytokines and chemokines coordinate the immune response

Anti - Inflammatories

Cyclooxygenase (COX)

- Cyclooxygenase (COX) is responsible for the formation of prostaglandins, prostacyclin and thromboxane.
- There are 3 type: COX-1, COX-2, COX-3
- COX -1 is constitutive and found in tissue
- COX-2 is inducible, hence it becomes abundant when activated by macrophages and other cells at inflammation site
- COX -3 located in the brain, which paracetemol acts on

Simpler Terms

COX-1



Maintain stomach lining



Promote renal blood flow



Alter platelet aggregation

COX-2

- Vasodilation and increase blood flow and redness
- Oedema and swelling
- Increased pain sensation
- Fever

NSAID

- Include a wide range of drugs with different chemical structure but similar pharmacological effects:
 - Antipyretic – reduce temperature
 - Analgesia – reduce sensation of pain
 - Anti –inflammatory – reduce inflammation
- These 3 effects result from the inhibition of cyclooxygenase.
- This then inhibits prostaglandins and thromboxane. However, can tilt thromboxane mechanism causing clotting.

- **Non Selective COX inhibitors**

- Non competitive
 - Aspirin
- Competitive
 - Phenylbutazone
 - Ibuprofen
 - Naproxen
 - Diclofenac
 - Piroxicam
 - Ketorolac

- **Analgesic with Antipyretic without anti inflammatory action**

- Paracetamol
- Metamizol
- Nefopam

- **Preferential COX – 2 inhibitors**

- Nimesulide
- Meloxicam
- Nabumetone

- **Selective COX -2 inhibitors**

- Celecoxib
- Rofecoxib
- Valdecoxit
- Etoricoxit
- Parecoxib
- Lumoracoxib

COX inhibitors

MECHANISM OF ACTION

Non-steroidal anti-inflammatory drugs (NSAIDs)

- All NSAIDs inhibit the cyclooxygenase required for conversion of arachidonic acid to endoperoxide intermediate (PGG2 and PGH2).
- NSAIDs inhibit prostaglandin and thromboxane synthesis, they are potent inhibitors of cyclooxygenase and eliminate all prostaglandins and thromboxanes in every cell they reach
- Recall that prostaglandins and thromboxanes play crucial roles in: Pain, Inflammation, Fever , Excessive blood clotting

Need of Selective COX -2 Inhibitors



inhibition of COX-2 - anti-inflammatory effects



inhibition of COX-1 - recognized toxicities of NSAIDs,

- a) peptic ulcers and the associated risks of bleeding, perforation and obstruction
- b) prolonged bleeding time
- c) renal insufficiency



inflamed tissues target without disturbing the homeostatic functions of prostaglandins in non-inflamed organs.



Theoretically, selective COX-2 inhibition should preserve the anti-inflammatory efficacy

Rise of COXIBS

- Large scale trials showed equal efficacy and lower GI side effects
- Market taken by a storm
- Celecoxib and then Rofecoxib became billion dollar drugs
- Extensive chronic usage in Inflammatory disorders like RA, Osteoarthritis and other Inflammatory disorders
- Newer Applications : Adenomas

Disturbing Reports from the long term trials of the Coxibs

CLASS AND VIGOR TRIALS

RISE IN CVS EVENTS!!!

What the FDA Says

- **Neutral:** “Celecoxib requires further study to estimate longer-term CV risks...”
- **Positive:** “There does not appear to be any clinically or statistically significant trend with celecoxib to suggest additional cardiovascular risks over the comparator drugs.”
- **Negative (almost):** “Some studies appear to show an increased risk of CV events, but the findings are not consistent across the COX-2 selective NSAIDs.”



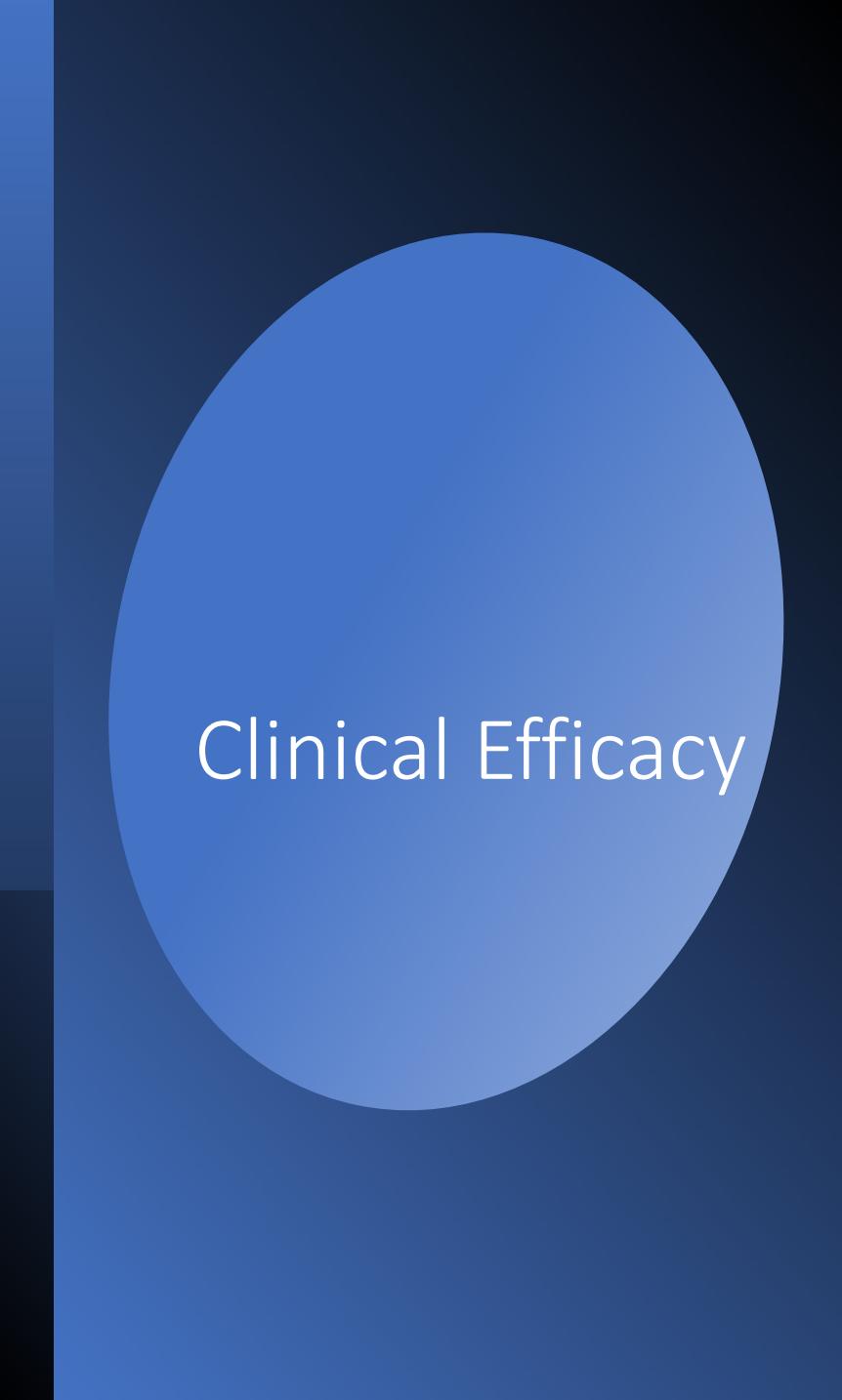
CLASS Trial: Conclusions

- ◆ *GI risk is lower than NSAIDs*
- ◆ *No significant difference between NSAIDs and Celecoxib for CV risk*



Black box warning : Valdecoxib

- Contraindicated in CABG patients
- Serious skin reaction : Steven Johnson syndrome and erythema multiforme
- Discontinue after first skin rash or mucosal lesion



Clinical Efficacy

- Osteoarthritis (OA), Rheumatoid Arthritis (RA), chronic low back pain, acute gouty arthritis, acute pain, and ankylosing spondylitis
- Efficacy demonstrated by statistically significant improvements in 3 areas
 - **1. Physical Function**
 - **2. Pain Subscale**
 - **3. Patient Evaluation**

Renovascular Safety

- Inhibition of renal prostaglandin synthesis
- complicates renal blood flow -> impaired kidney function
 1. fluid retention (edema)
 2. hypertension
 3. Congestive Heart Failure
- Oedema, hypertension, and CHF were mild and infrequently led to discontinuations

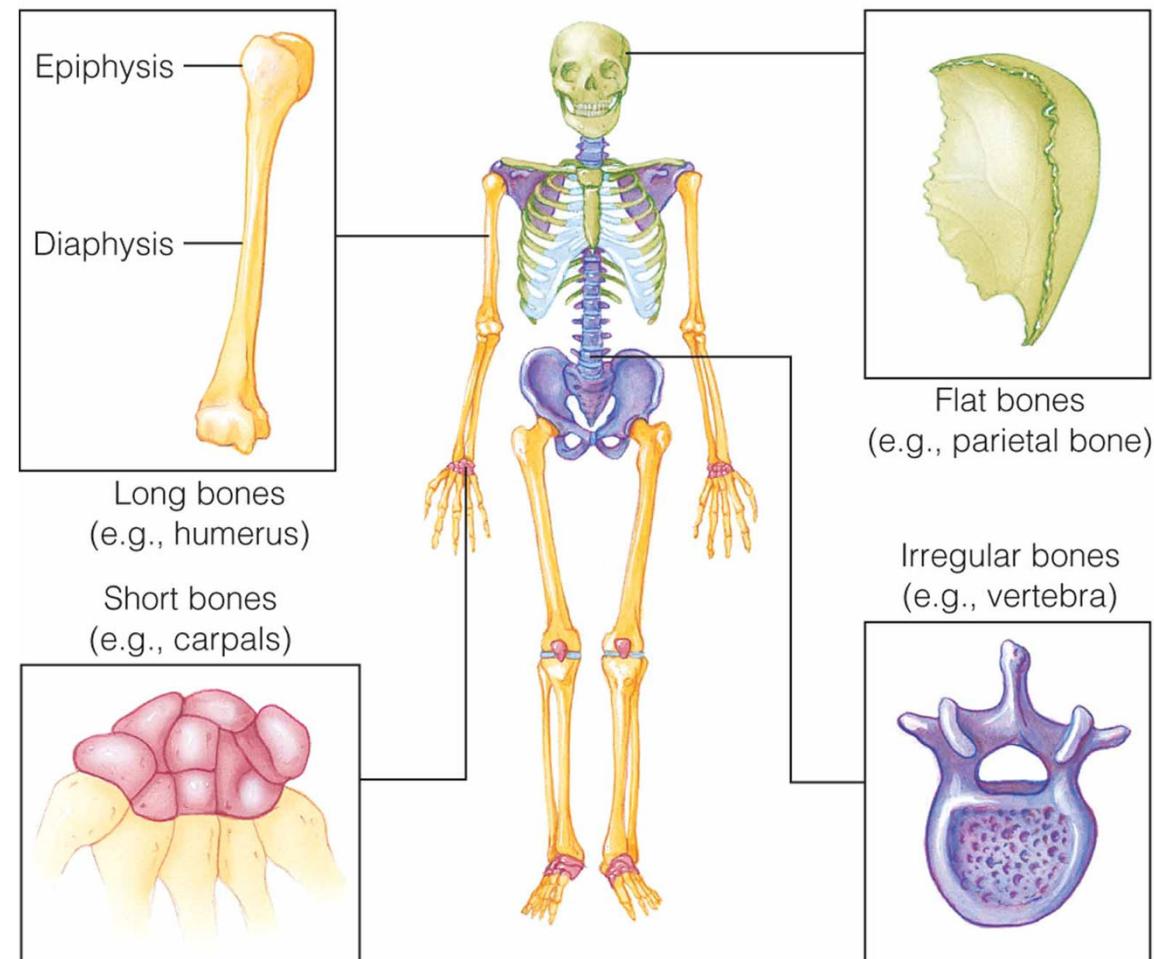
Generally consistent with rates observed for nonselective NSAIDs

Side Effect Profile

- Normal therapeutic dose does not appear to affect COX-1 enzyme
- Generally **lower incidence of gastrointestinal ulceration and bleeding** compared to nonselective NSAIDs
- Avoids respiratory depression and other common opioid side affects

Musculoskeletal Overview and some Disorders

Figure 41-2 Classification of bones by shape.



Skeletal System

- Bone types
- Bone structure
- Bone function
- Bone growth and metabolism affected by calcium and phosphorous, calcitonin, vitamin D, parathyroid, growth hormone, glucocorticoids, estrogens and androgens, thyroxine, and insulin.

Bone Marrow

Red bone marrow

- Found in flat bones of sternum, ribs, and ileum
- Produces blood cells and hemoglobin

Yellow bone marrow

- Found in shaft of long bones
- Contains fat and connective tissue

Changes in Older Adult

- Loss of bone mass in older women
- Joint and disk cartilage dehydrates causing loss of flexibility contributes to degenerative joint disease (osteoarthritis); joints stiffen, lose range of motion

Changes in Older Adult

- Cause stooped posture, changing center of gravity
- Elderly at greater risk for falls
- Endocrine changes cause skeletal muscle atrophy
- Muscle tone decreases

Assessment

- Examine complaints of pain for location, duration, radiation character (sharp dull), aggravating, or alleviating factors
- Inquire about fever, fatigue, weight changes, rash, or swelling

HISTORY

Pc	HPC
PMH	Meds
Allergies	Social History
Family History	Systems Overview

If injury
Mechanism of Injury
Type of trauma
First Aid

Other symptom considerations

- Swelling
- Limitation ROM
- Deformity
- Instability

- Inflammatory/Non inflammatory
- Treatments

MORE HISTORY

- Past Medical History
 - Cancer
 - Diabetes
 - DVT/ PE
- Social History
- Family History
- Medications (NSAID)
- Allergies (PCN)
- Immunizations: Tetanus
- Review of Systems
 - Fever, chills, sweats
 - Weight loss
 - Increased pain at night or with rest
 - Numbness/ Weakness



SYMPTOM ANALYSIS

- Pain
- Weakness
- Deformity
- Limited ROM
- Stiffness
- Clicking

Pain

- *Onset*
- *Location: "point with a finger"*
- *Intensity/ Quality: 0 – 10*
- *Timing*
 - *Frequency, Duration*
 - *Relation to activity*
 - *Mechanical vs Inflammatory*
- *Aggravating conditions*
- *Prior treatment*

- When does it occur
- Tendinitis and Rheumatoid Arthritis - bad in the AM
- Osteoarthritis - worse as day progresses
- Onset
 - Sudden - Fracture, sprain, gout, trauma, septic joint
 - Gradual - Tendonitis, tumor,
- One or multiple joint



PAIN

DEFORMITY STIFFNESS

- Trauma (fracture, dislocation, tendon tear)
- Osteogenesis imperfecta
- Rheumatic nodules
- Scoliosis
- Tumour
- OA osteophytes
- Rheumatoid arthritis
Stiff upon waking and after rest.
- Osteoarthritis
Stiffness in the AM resolves faster than RA

CLICKING



Usually not significant if no pain



However, associated pathologies:

Meniscus tear, TMJ

Subluxing tendon (I.e. peroneal or biceps)

Dislocating/ subluxing joint

Musculoskeletal Disorders

Variety of drug are used in the treatment of bone and muscle disorders

Drug selected on basis of

- Disorder
- Severity
- Patients response to past therapy

Musculoskeletal Conditions

- Osteoarthritis
- Rheumatoid Arthritis
- Gout
- Osteoporosis
- Ankylosing Spondylitis
- Pagets Disease

Osteoarthritis

Osteoarthritis is an idiopathic disease

Characterized by degeneration of articular cartilage

Leads to fibrillation, fissures, gross ulceration and finally disappearance of the full thickness of articular cartilage

What is Osteoarthritis?

Osteoarthritis is a form of arthritis that features the breakdown and eventual loss of the cartilage of one or more joints.

Cartilage is a protein substance that serves as a "cushion" between the bones

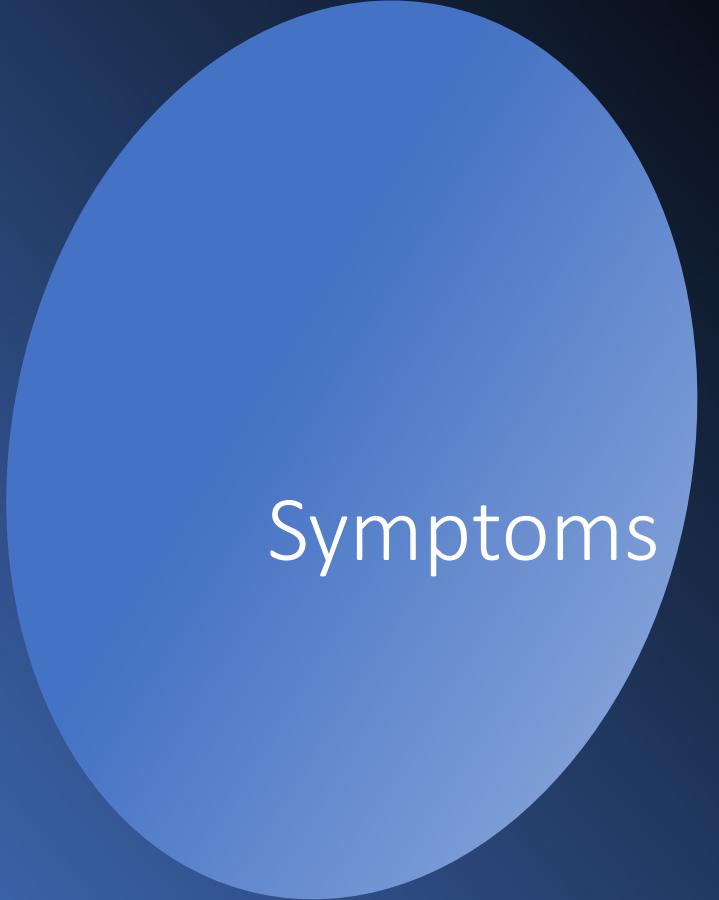
Primary Osteoarthritis

Osteoarthritis not resulting from injury or disease, is mostly a result of natural aging of the joint.

With aging, the water content of the cartilage increases, and the protein makeup of cartilage degenerates..

Secondary Osteoarthritis

- is a form of osteoarthritis that is caused by another disease or condition. include obesity, repeated trauma or surgery to the joint structures, abnormal joints at birth (congenital abnormalities), gout, diabetes, and other hormone disorders.



Symptoms

- Develop slowly
- Pain and sore over certain joints during inactivity
- Stiff, creaky affected joints
- Morning stiffness that resolves after 30 minutes

- Develops in the weight-bearing joints of the knees, hips, or spine. It's also common in the fingers, thumb, neck, and big toe. Other joints are usually not affected, unless an injury is involved



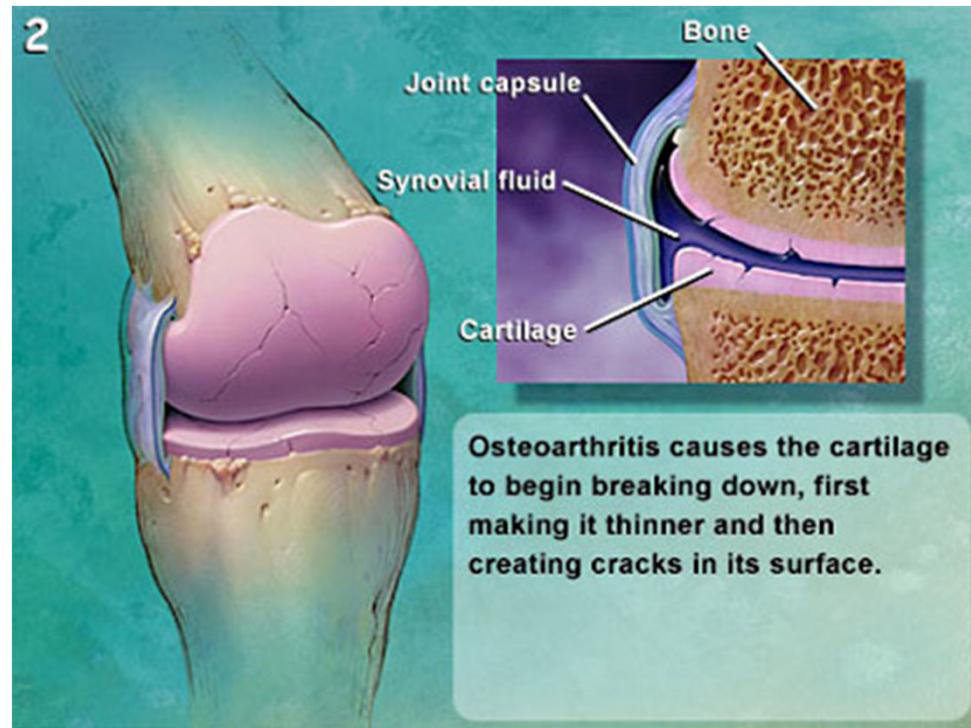
Osteoarthritis

- The most common symptom of osteoarthritis is pain in the affected joint(s) after repetitive use.
- There is no blood test for the diagnosis of osteoarthritis.
- The goal of treatment in osteoarthritis is to reduce joint pain and inflammation while improving and maintaining joint function.

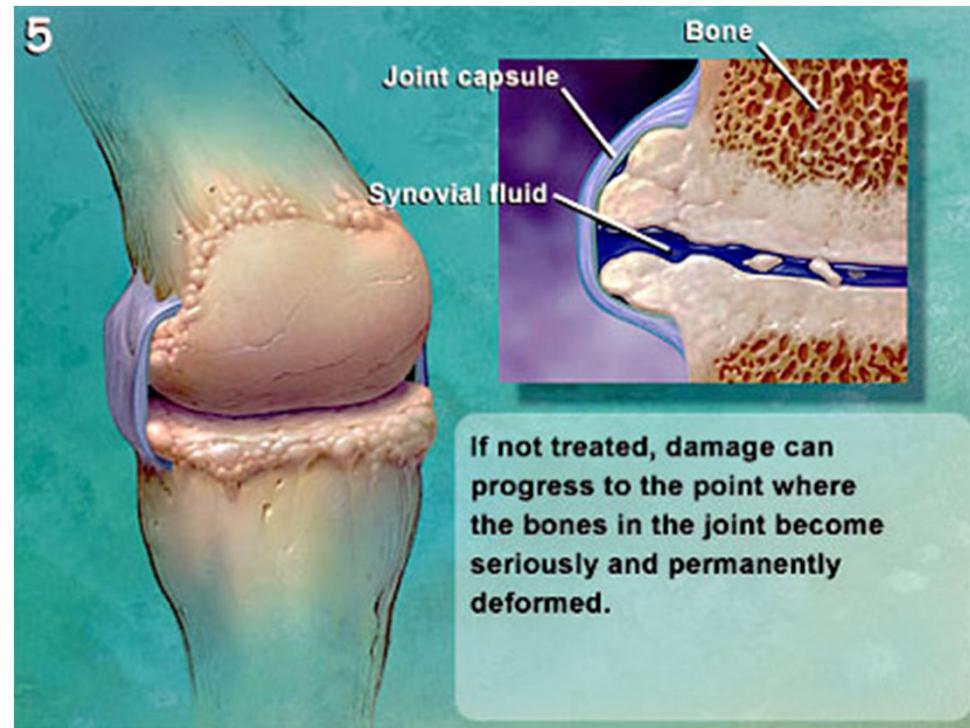


Factors responsible

- Ageing
- Genetics
- Hormones
- Mechanics



Osteoarthritis



Osteoarthritis

Management of OA

- Establish the diagnosis of OA on the basis of history and physical and x-ray examinations
- Decrease pain to increase function
- Prescribe progressive exercise to
 - Increase function
 - Increase endurance and strength
 - Reduce fall risk
- Patient education: Self-Help Course
 - Weight loss
 - Heat/cold modalities

Exercise and Weight Loss



Exercise:

One of the most effective ways to help arthritis!

Helps reduce stiffness, increases flexibility and prevents falls



Weight Loss:

Research studies have shown that even a 10% loss of weight can improve OA symptoms by 50%!!

Pharmacologic Management of OA

- Nonopioid analgesics
- Topical agents
- Intra-articular agents
- Opioid analgesics
- NSAIDs
- Unconventional therapies



Topical Treatments

- There are a variety of things that can be applied to the affected joint that will relieve pain:
 - Heat and ice
 - Lidocaine patches
 - Topical NSAIDS (not for long-term relief)
 - Capsaicin (Zostrix)
 - A skin cream made from hot peppers that relieves pain and possibly reduces inflammation over time

Are NSAIDs Safe?

- In general, NSAIDS are good class of drugs because they treat pain and reduce inflammation
- Negative side effects:
 - Non-selective NSAIDS
 - Stomach upset/bleeding/ulcers
 - Selective “COX-2” drugs:
 - Possibly increase heart attack/disease risk



The Clock is Ticking...

Studies show that Topical NSAIDs used in OA are only effective during the first 2 weeks of therapy!!

BIPHOSPHONATES

- Inhibit osteoclast-mediated bone resorption
- Increases BMD and total bone mass
- *Fosamax 5 mg daily or 35 mg/wk prevention
10 mg daily or 75 mg/wk treatment
- *Instructions on administration: AM first thing, full glass of water, do not eat or drink for 30 minutes, sitting up
These precautions aid in absorption and decrease GI side effects i.e. gastritis, weight loss, anorexia, esophageal irritation.

Corticosteroids

- These drugs are naturally occurring substances in the body but as drugs they have been further refined to make them more effective. Examples:
 - Prednisone , Hydrocortisone, Betamethasone, Methylprednisolone, Triamcinolone,etc
- They can be used orally or by injection for OA. They have significant side effects so they should be used sparingly (intra-articular injection every 3-6 months)
- What other effects do corticosteroids have.

Treatment: Calcitonin

Potent inhibitor of osteoclast function
Produces rapid decrease in bone resorption
Weaker effect on bone mass than other available agents
PROOF study did not show reduction in
vertebral fractures

Treatment: Alendronate

Most potent drug currently available for treatment
of osteoporosis

Inhibits osteoclast-mediated bone resorption

FIT results:

- New vertebral fractures reduced by 50%
- Hip fractures reduced by 56%¹

Meta-analyses show consistent reductions in hip
fractures of approximately 50%²

Treatment: Parathyroid Hormone (PTH)

Principal regulator of calcium homeostasis
Stimulates bone formation
Used alone or in combination with anti-resorptive agents
Potent effect on fractures: reduction of 65 - 69% in vertebral fractures and 35 - 45% in nonvertebral fractures¹



OA: Unconventional Therapies

Polysulfated
glycosaminoglycans—
nutraceuticals

- Glucosamine +/- chondroitin sulfate: Symptomatic benefit, no known side effects, long-term controlled trials pending

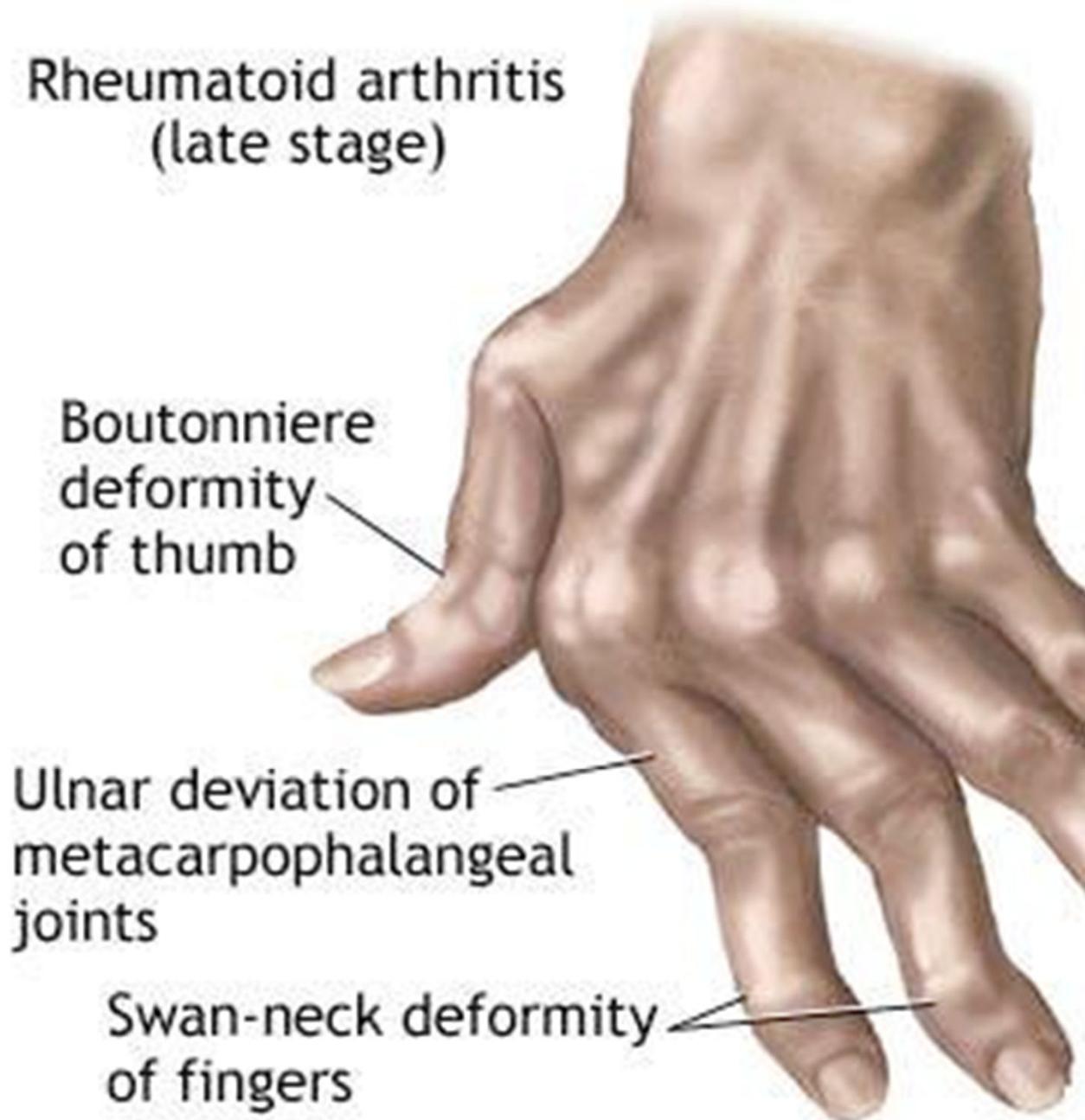
Tetracyclines as
protease/cytokine
inhibitors

- Under study
- Have disease-modifying potential

Rheumatoid Arthritis



Rheumatoid arthritis (late stage)



Rheumatoid arthritis

- Chronic disease affecting synovial joints.
- Commonly affects hands and wrists
- Bilateral swelling, stiffness and pain in joints
- 3 times more common in females than men.
- Usually starts 30-50yrs age
- Rheumatoid factor found later

- Symptoms >6 weeks' duration
 - Often lasts the remainder of the patient's life
- Inflammatory synovitis
 - Palpable synovial swelling
 - Morning stiffness >1 hour, fatigue
- Symmetrical and polyarticular (>3 joints)
 - Typically involves wrists, MCP, and PIP joints
 - Typically spares certain joints
 - Thoracolumbar spine
 - DIPs of the fingers and IPs of the toes

RA:Key Features

- Symptom duration >6weeks
- Early morning stiffness >1hr
- Three or more regions affected
- Bilateral compression tenderness MTPJ
- Symmetry of areas affected
- Bony erosions on x-ray late in disease

RA : Key diagnostic criteria

RA :Symptoms

- insidious onset with fever, malaise, fatigue, anorexia, vague joint pain
- at first pain occurs only upon moving the joint, later pain is constant
- decreased joint mobility
- joint deformities
- rheumatoid nodules

*** Cause of RA is unclear. Some evidence that it is immune related.

RA: Pathogenesis

Synovium

- is a thin membrane that provides a physical barrier prevent things entering joint space
- Cells within produce fluids allowing joint to move freely by keeping bones apart
- Provides nutrients to cartilage

RA: Typical Course

Damage occurs early in most patients

- 50% show joint space narrowing or erosions in the first 2 years
- By 10 years, 50% of young working patients are disabled

Death comes early

- Multiple causes
- Compared to general population
 - Women lose 10 years, men lose 4 years

Rheumatoid Arthritis:Treatment Principles

- Confirm the diagnosis
- Determine where the patient stands in the spectrum of disease
- When damage begins early, start aggressive treatment early
- Use the safest treatment plan that matches the aggressiveness of the disease
- Monitor treatment for adverse effects
- Monitor disease activity, revise Rx as needed

Critical Elements of a Treatment Plan: Assessment

- Assess current activity
 - Morning stiffness, synovitis, fatigue, ESR
- Document the degree of damage
 - ROM and deformities
 - Joint space narrowing and erosions on x-ray
 - Functional status
- Document extra-articular manifestations
 - Nodules, pulmonary fibrosis, vasculitis
- Assess prior Rx responses and side effects

Disease modification

- SAARD – slow acting antirheumatic drugs
- DMARD – disease modifying antirheumatic drugs

Penicillamine

- **Penicillamine** has a similar action to gold, and more patients are able to continue treatment than with gold but side-effects occur frequently.
- Patients should be warned not to expect improvement for at least 6 to 12 weeks after treatment is initiated. Penicillamine should be discontinued if there is no improvement within 1 year.
- Nausea may occur but is not usually a problem provided that penicillamine is taken before food or on retiring and that low initial doses are used and only gradually increased. Loss of taste may occur about 6 weeks after treatment is started but usually returns 6 weeks later irrespective of whether or not treatment is discontinued; mineral supplements are not recommended. Rashes are a common side-effect. Those which occur in the first few months of treatment disappear when the drug is stopped and treatment may then be re-introduced at a lower dose level and gradually increased. Late rashes are more resistant and often necessitate discontinuation of treatment.
- Patients who are hypersensitive to penicillin may react rarely to penicillamine.

Antimalarials

- The antimalarial **hydroxychloroquine** is used to treat rheumatoid arthritis of moderate inflammatory activity; **chloroquine** is also licensed for treating inflammatory disorders but it is used much less frequently and it is generally reserved for use if other drugs have failed.
- These drugs are effective for mild systemic lupus erythematosus, particularly involving cutaneous and joint manifestations.
- Chloroquine and hydroxychloroquine should not be used for psoriatic arthritis.
- Chloroquine and hydroxychloroquine are better tolerated than gold or penicillamine. Retinopathy (see below) occurs rarely provided that the recommended doses are not exceeded; in the elderly it is difficult to distinguish drug-induced retinopathy from ageing changes.

Drugs affecting the immune response

- **Methotrexate** is a disease-modifying antirheumatic drug suitable for moderate to severe rheumatoid arthritis. **Azathioprine, ciclosporin, cyclophosphamide, leflunomide**, and the **cytokine inhibitors** are considered more toxic and they are used in cases that have not responded to other disease-modifying drugs.
- **Methotrexate** is usually given in an initial dose of 7.5 mg by mouth once a week, adjusted according to response to a maximum of 15 mg once a week (occasionally 20 mg once a week).
- **Azathioprine** is usually given in a dose of 1.5 to 2.5 mg/kg daily in divided doses. Blood counts are needed to detect possible neutropenia or thrombocytopenia (usually resolved by reducing the dose). Nausea, vomiting, and diarrhoea may occur, usually starting early during the course of treatment, and may necessitate withdrawal of the drug; herpes zoster infection may also occur.

DMARDs Have a Dark Side



Don't Miss It

*DMARDs have a dark side
Methotrexate may cause
serious problems*

Lung

Liver

Bone marrow

*Be on the look out for toxicity
with all the DMARDs*

Methotrexate Lung



Dry cough, shortness of breath, fever



Most often seen in the first 6 months of MTX treatment



Diffuse interstitial pattern on x-ray

Bronchoalveolar lavage may be needed to rule out infection



Acute mortality = 17%; 50% to 60% recur with retreatment, which carries the same mortality



Risk factors: older age, RA lung, prior use of DMARD, low albumin, diabetes



Clues for C1-C2 Subluxation

Long-standing rheumatoid arthritis or JRA

May have NO symptoms

C2-C3 radicular pain in the neck and occiput

Spinal cord compression

- Quadriplegia or paraparesis
- Sphincter dysfunction
- Sensory deficits
- TIAs secondary to compromise of the vertebral arteries

RA: NSAID Gastropathy

Don't Miss It

- NSAID gastropathy is sneaky and can be fatal
- Gastric ulcers are more common than duodenal ulcers
- No reliable warning signs
- 80% of serious events occur without prior symptoms
- Risk of hospitalization for NSAID ulcers in RA is 2.5 to 5.5 times higher than general population



- Choose a treatment plan with enough power to match the disease
 - If in doubt, get some help
 - Rheumatologists can be a bargain
 - New classes of drugs and biologics offer new opportunities
- Do no harm
 - Monitor for drug toxicity—high index of suspicion and routine monitoring
 - Alter the treatment based on changes in disease activity

RA: Summary

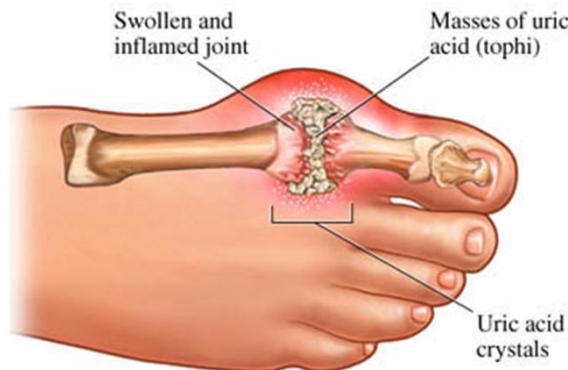
Gout - acute arthritis

*acute synovitis
ankle & first
joints*



© ACR

Gout



- Painful arthritic disease that occurs most often in men
- Disruption of body's control over uric acid production or excretion, resulting in high levels of uric acid in the blood
- When uric acid builds to a certain level, it crystallizes, and these crystals are deposited in connective tissue all over the body
- When crystals are deposited in the synovial fluid, they cause sudden sharp pain in the joint

Gouty arthritis - characteristics

sudden onset

- recurrent episodes
- influenced by diet
- bony erosions on Xray

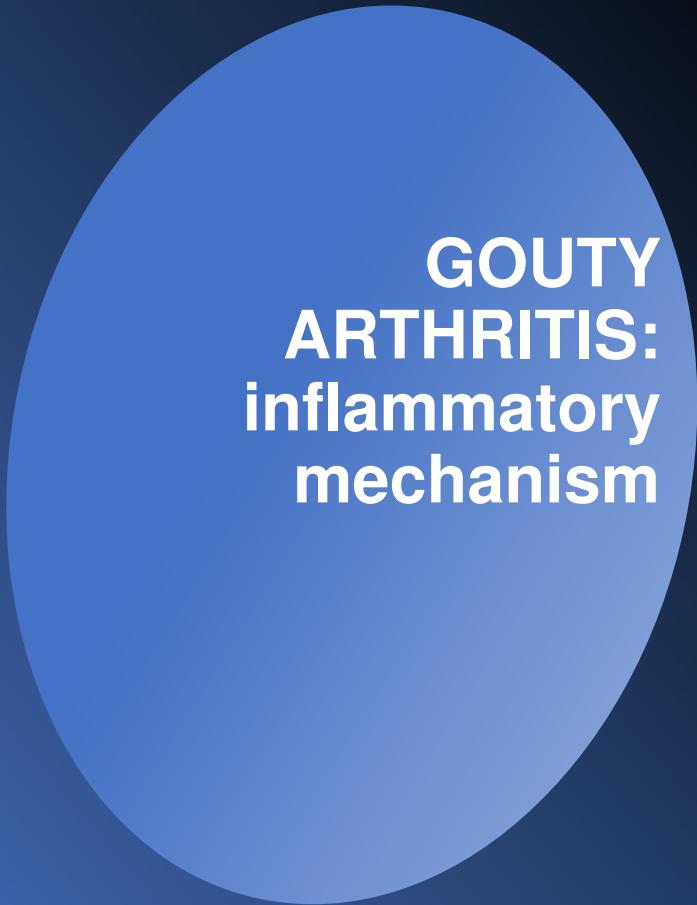
middle aged males

severe pain

distal joints

Intense inflammation





GOUTY ARTHRITIS: inflammatory mechanism

Body fluids supersaturate with urate and urate crystals precipitate in tissues.

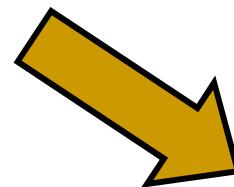
- Resulting in pain and inflammation

Phagocytosis of crystals by polymorphs and the migration of leukocytes to the inflamed area

- Release inflammatory mediators into joint

Gout - tophus

- *classic location of tophi on helix of ear*



Gout - X-ray changes

DIP joint destruction

*phalangeal bone
cysts*



Gout Management Approach

INITIATE

(acute flare)



- *Treat acute flare rapidly with anti-inflammatory agent*

RESOLVE

(urate-lowering therapy)



- *Initiate urate-lowering therapy to achieve sUA <6*
- *Use concomitant anti-inflammatory prophylaxis for up to 6 mo to prevent mobilization flares*

MAINTAIN

(treatment to control sUA)



- *Continue urate lowering therapy to control flares and avoid crystal deposition*
 - *Prophylaxis use for at least 3-6 months until sUA normalizes*
-

Treating acute gouty arthritis

- colchicine
- NSAID's
- steroids
- rest, analgesia, ice, time

Colchicine - plant alkaloid



- *colchicum autumnale*
- (*autumn crocus or meadow saffron*)

Colchicine

- “only effective in gouty arthritis”
 - not an analgesic
 - does not affect renal excretion of uric acid
 - does not alter plasma solubility of uric acid
 - neither raises nor lowers serum uric acid
 - mechanism of action poorly understood
 - reduces inflammatory response to deposited crystals
 - diminishes PMN phagocytosis of crystals
 - blocks cellular response to deposited crystals
-

Gout - colchicine therapy

more useful for daily prophylaxis (low dose)

- prevents recurrent attacks
- colchicine 0.6 mg qd - bid

declining use in acute gout (high dose)

- prevents arthritis, tophi & stones by lowering total body pool of uric acid
- not indicated after first attack
- initiation of therapy can worsen or bring on acute gouty arthritis
- no role to play in managing acute gout

Drug therapy of gout

*Drugs That Block
Production of Uric Acid*



Allopurinol

- 90% absorption from the gut
- metabolized to oxypurinol
- once daily dosing
- lowers serum uric acid levels
- lowers urine uric acid levels
- side effects rare, but potentially lethal

Allopurinol – black box warning



THIS IS NOT AN INNOCUOUS DRUG. IT IS NOT RECOMMENDED FOR THE TREATMENT OF ASYMPTOMATIC HYPERURICEMIA



ALLOPURINOL SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS OF AN ALLERGIC REACTION

Stevens-Johnson syndrome

- *target skin lesions*
- *mucous membrane erosions*
- *epidermal necrosis with skin detachment*



Febuxostat

- recently approved by FDA (not on market)
- oral xanthine oxidase inhibitor
- chemically distinct from allopurinol
- 94% of patients reached urate < 6.0 mg/dl
- minimal adverse events
- can be used in patients with renal disease

Drug therapy of gout

*Drugs That Enhance
Excretion of Uric Acid*



Gout - rule

“Don’t mess with the uric acid level”

*Don’t change your urate-lowering
therapy during an acute gout attack*

Take Home Points

- Goal sUA < 6, and use concurrent prophylaxis
- Colchicine has FDA-approved dosing guidelines for chronic kidney disease
- Febuxostat is an excellent alternative for patients with renal insufficiency
- Other treatment alternatives exist, please refer to rheumatologist for difficult cases

Categorization of Pain Conditions

Nociceptive Pain



(ie, Burn)

Noxious stimuli

Neuropathic Pain



(ie, Herpes zoster)

Neuronal damage

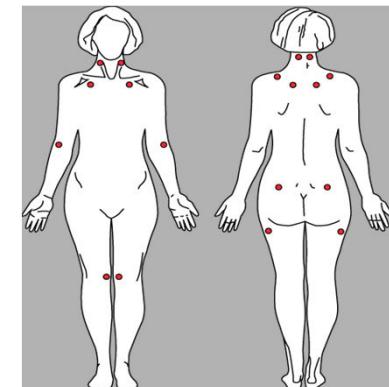
Inflammatory Pain



(ie, Rheumatoid arthritis)

Inflammation

Central Pain Amplification



(ie, Fibromyalgia)

Abnormal pain processing by CNS

Acute Pain

Chronic Pain

Fibromyalgia (FM): A Chronic Widespread Neurologic Pain Condition

- FM is a neurological condition associated with chronic widespread pain (CWP) and tenderness
- American College of Rheumatology (ACR) criteria for the diagnosis of FM:
 - Chronic widespread pain
 - Pain for ≥ 3 months
 - Pain above and below the waist
 - Pain on left and right sides of body and axial skeleton
 - Pain at ≥ 11 of 18 tender points when palpated with 4 kg of digital pressure

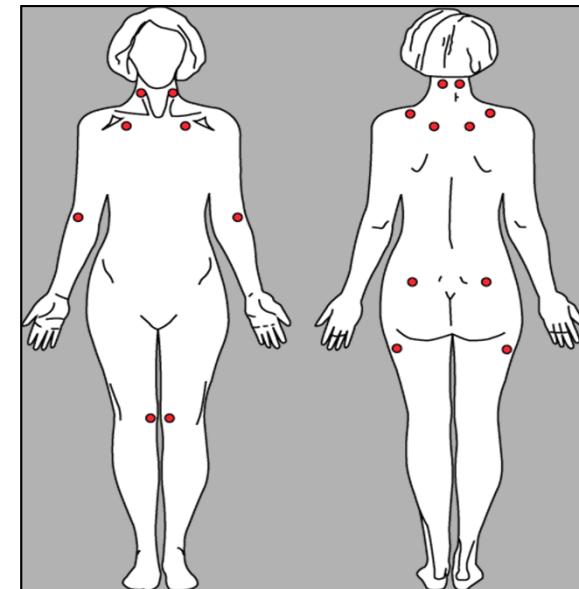


Diagram showing 18 tender points

ACR criteria are both sensitive (88.4%) and specific (81.1%)²

Risk Factors for FM

- Genetic factors
 - Relatives of FM patients are at higher risk for FM
 - First-degree relatives are significantly more likely to have FM (Odds ratio=8.5; $P =0.0002$)
 - Have significantly more tender points
- Environmental factors
 - Physical trauma or injury
 - Infections (Lyme disease, hepatitis C)
 - Other stressors (eg, work, family, life-changing events)
- Gender
 - Women are diagnosed with FM about 7 times as often as men

1. Arnold LM, et al. *Arthritis Rheum.* 2004;50(3):944-952.

2. Mease PJ. *J Rheumatol.* 2005;32(suppl 75):6-21.

3. Arnold LM, et al. *Arthritis Rheum.* 2004;50(9):2974-2984.

Fibromyalgia :Summary

- FM is one of the most common chronic widespread neurologic pain conditions¹
 - Associated with hyperalgesia and allodynia²
 - Central sensitization is a leading theory to explain FM³
 - Demonstrated by excessive release of the pain neurotransmitters³ glutamate and substance P
- FM is commonly seen with other chronic pain-related conditions⁴
- ACR criteria for the diagnosis of FM are sensitive and specific⁵
 - History of CWP \geq 3 months
 - Pain in 4 quadrants and axial skeleton
 - \geq 11 of 18 tender points
- FM diagnosis is a key to successful management⁶

1. Wolfe F, et al. *Arthritis Rheum.* 1995;38(1):19-28.

2. Gottschalk A and Smith DS. *Am Fam Physician.* 2001;63:1979-1984.

3. Staud R and Rodriguez ME. *Nat Clin Pract Rheumatol.* 2006;2:90-98.

4. Weir PT, et al. *J Clin Rheumatol.* 2006;12(3):124-128.

5. Wolfe F, et al. *Arthritis Rheum.* 1990;33:160-172.

6. Goldenberg DL, et al. *JAMA.* 2004;292:2388-2395.

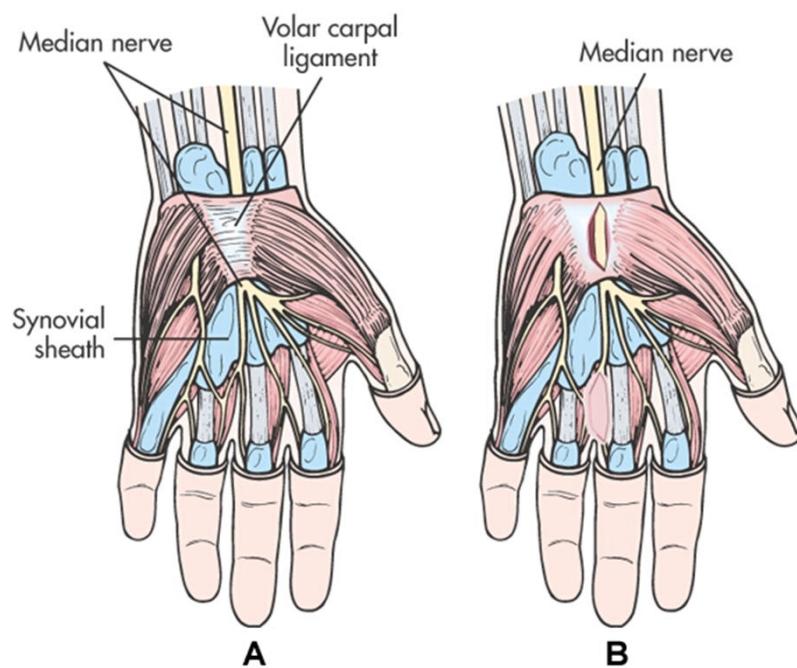
Carpal Tunnel Syndrome

- Median nerve is compressed; sensation and circulation to thumb and fingers is compromised
- Usually in women ages 30-60
- Increasing incidence
- Predisposing factors
 - Repetitive hand and wrist motions
 - Pregnancy
 - Diabetes mellitus
 - Menopause
 - RA
 - Dislocation or acute sprain

Carpal Tunnel Syndrome

A, Wrist structures involved in carpal tunnel syndrome.

B, Decompression of median nerve.



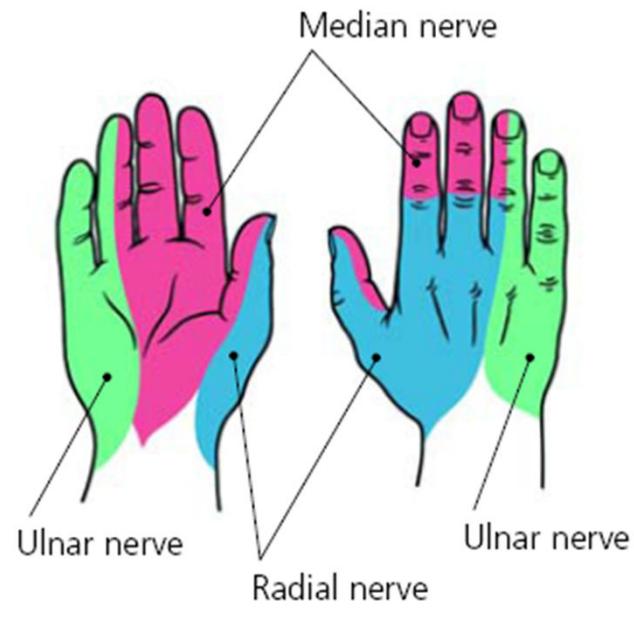
From Thompson JM et al: *Mosby's clinical nursing*, ed 5, St. Louis, 2002, Mosby.
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Definition

- Carpal tunnel syndrome, the most common focal peripheral neuropathy, results from compression of the median nerve at the wrist.

Clinical Features

- Pain
- Numbness
- Tingling
- Symptoms are usually worse at night and can awaken patients from sleep.
- To relieve the symptoms, patients often “flick” their wrist as if shaking down a thermometer (flick sign).



Treatment



CONSERVATIVE TREATMENTS

GENERAL MEASURES

WRIST SPLINTS

ORAL MEDICATIONS

LOCAL INJECTION

ULTRASOUND THERAPY

Predicting the Outcome of Conservative Treatment



SURGERY

GENERAL MEASURES

- Avoid repetitive wrist and hand motions that may exacerbate symptoms or make symptom relief difficult to achieve.
- Not use vibratory tools
- Ergonomic measures to relieve symptoms depending on the motion that needs to be minimized

WRIST SPLINTS



ORAL MEDICATIONS



- Diuretics
 - Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - pyridoxine (vitamin B6)
 - Orally administered corticosteroids
 - Prednisolone
 - 20 mg per day for two weeks
 - followed by 10 mg per day for two weeks

LOCAL INJECTION

- A mixture of 10 to 20 mg of lidocaine (Xylocaine) without epinephrine and 20 to 40 mg of methylprednisolone acetate (Depo-Medrol) or similar corticosteroid preparation is injected with a 25-gauge needle at the distal wrist crease (or 1 cm proximal to it).

SURGERY

- Should be considered in patients with symptoms that do not respond to conservative measures and in patients with severe nerve entrapment as evidenced by nerve conduction studies,thenar atrophy, or motor weakness.
- It is important to note that surgery may be effective even if a patient has normal nerve conduction studies

Carpal Tunnel : Summary

- Conservative treatment options include splinting the wrist in a neutral position and ultrasound therapy
- Orally administered corticosteroids can be effective for short-term management (two to four weeks), but local corticosteroid injections may improve symptoms for a longer period.
- If symptoms are refractory to conservative measures or if nerve conduction studies show severe entrapment, open or endoscopic carpal tunnel release may be necessary.

Metabolic Bone Disorders

- **Osteoporosis**
- **Osteomalacia**
- **Paget's Disease**

Osteoporosis

- A disease in which loss of bone exceeds rate of bone formation; usually increase in older women, white race, nulliparity.
- Clinical Manifestations – bone pain, decrease movement.
- Treatment – Calcium, Vit. D, estrogen replacement, Calcitonin, fluoride, estrogen with progestin, SERM (**Selective Estrogen Receptor Modulator**) with anti-estrogens, exercise.
- Pathologic fracture-safety.

Classification of Osteoporosis

- **Generalized osteoporosis occurs most commonly in postmenopausal women and men in their 60s and 70s.**
- **Secondary osteoporosis results from an associated medical condition such as hyperparathyroidism, long-term drug therapy, long-term immobility.**
- **Regional osteoporosis occurs when a limb is immobilized.**

Health Promotion/Illness Prevention - Osteoporosis

- **Ensure adequate calcium intake.**
- **Avoid sedentary life style (a type of lifestyle with a lack of physical exercise) .**
- **Continue program of weight-bearing exercises.**

Osteoporosis

Diet Therapy

- Protein
- Magnesium
- Vitamin K
- Trace minerals
- Calcium and vitamin D
- Avoid alcohol and caffeine

Drug Therapy

- Hormone replacement therapy
 - Parathyroid hormone
 - Calcium and vitamin D
 - Bisphosphonates
 - Selective estrogen receptor modulators
 - Calcitonin
 - Other agents used with varying results
-

Osteomalacia

- **Softening of the bone tissue characterized by inadequate mineralization of osteoid**
- **Vitamin D deficiency, lack of sunlight exposure**
- **Similar, but not the same as osteoporosis**
- **Major treatment: vitamin D from exposure to sun and certain foods**

Osteomyelitis

- A condition caused by the invasion by one or more pathogenic microorganisms that stimulates the inflammatory response in bone tissue
- Exogenous, endogenous, hematogenous, contiguous

Osteomyelitis

- **Infection of bone; causative agent – Staph/Strept**
- **Typical signs and symptoms :Acute osteomyelitis include:**
 - **Fever that may be abrupt**
 - **Irritability or lethargy in young children**
 - **Pain in the area of the infection**
 - **Swelling, warmth and redness over the area of the infection**
- **Chronic osteomyelitis include:**
 - **Warmth, swelling and redness over the area of the infection**
 - **Pain or tenderness in the affected area**
 - **Chronic fatigue**
 - **Drainage from an open wound near the area of the infection**
 - **Fever, sometimes**
 - **Treatment – IV antibiotic; long term for 4-6 months**

Bone Tumors

- **Benign bone tumors (noncancerous):**
 - **Chondrogenic tumors:** osteochondroma, chondroma
 - **Osteogenic tumors:** osteoid osteoma, osteoblastoma, giant cell tumor
 - **Fibrogenic tumors**



OSTEOCHONDROMA

- Cartilage capped exostosis
- Commonest benign tumour of bone
- Metaphyseal developmental abnormality

Osteosarcoma

- Cancer of the bone – metastasis to the lung is common. Most in long bones.
- Clinical manifestations – dull pain, swelling, intermittent but increases over time; night pain common.
- Treatment – radiation, chemotherapy, hormonal therapy, surgical excision with prosthetics, assistance devices, palliative measures.

Key messages – Pharmacotherapy

- Use paracetamol first, as it is effective when taken regularly in appropriate doses and has a good safety profile
- Before prescribing COX-2 selective or conventional NSAIDS, review risk of peptic ulcer, cardiac disease or renal impairment.
- COX-2 selective NSAIDS are not more effective than conventional NSAIDS and have a similar range of adverse effects.

Summary

THE END OF
MUSCULOSKELETAL

