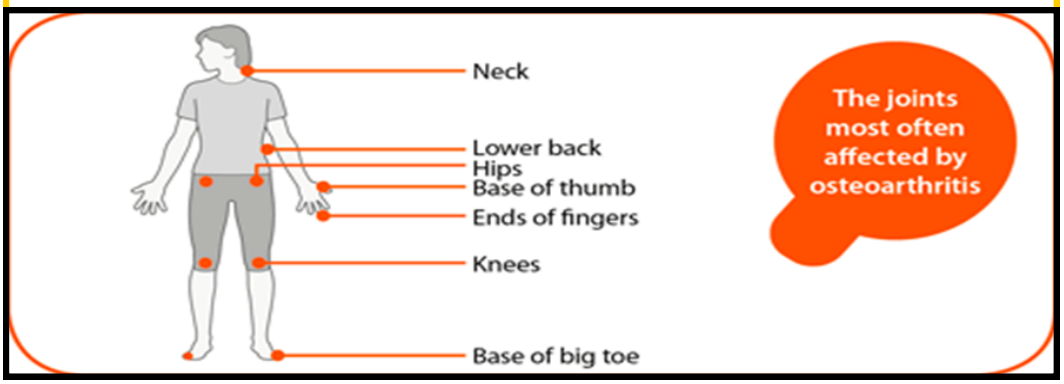
PHARMACY DEPARTMENT
HOSPITAL SEGAMAT

OSTEOARTHRITIS

INTRODUCTION

Osteoarthritis is a chronic disorder associated with damage to the cartilage and surrounding tissues and characterized by pain, stiffness, and loss of function. It is the most common joint disorder, often begins in the 40s and 50s. The disease occurs when the joint cartilage breaks down often because of mechanical stress or biochemical alterations, causing the bone underneath to fail. OA can occur together with other types of arthritis, such as gout or rheumatoid arthritis. OA tends to affect commonly used joints such as the hands and spine, and the weight-bearing joints such as the hips and knees. OA is classified as primary (or idiopathic) when the cause is not known (as in the large majority of cases) or secondary when the cause is another disease or condition, such as an infection, joint abnormality that appeared at birth or injury.[1]



PATHOPHYSIOLOGY

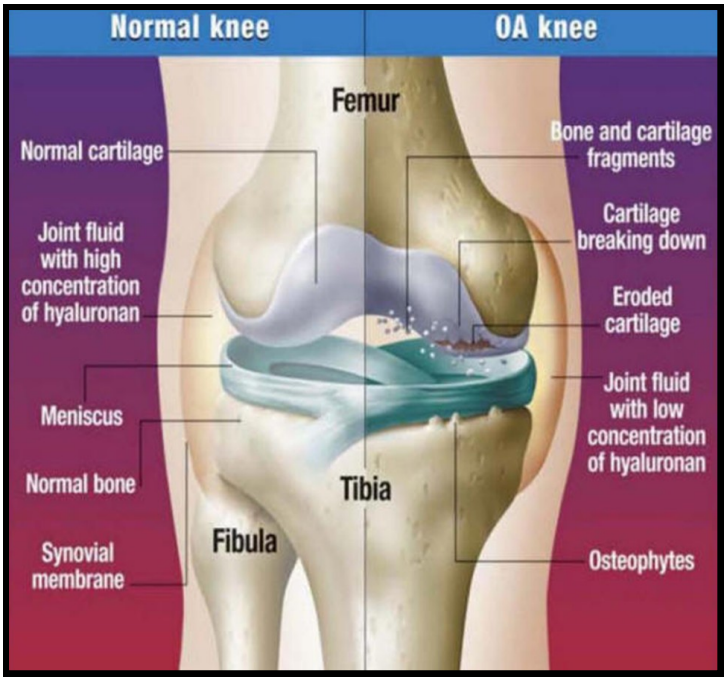
Normal synovial joints allow a significant amount of motion along their extremely smooth articular surface. These joints are composed of the following:

1. Articular cartilage
2. Subchondral bone
3. Synovial membrane
4. Synovial fluid

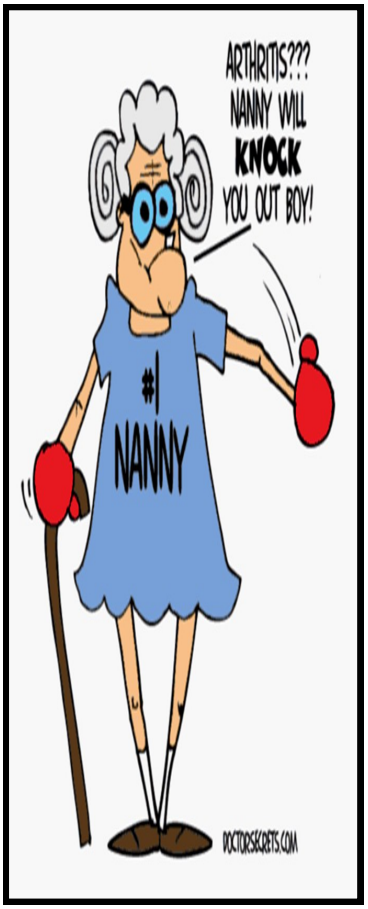
5. Joint capsule

The normal articular surface of synovial joints consists of articular cartilage (composed of chondrocytes) surrounded by an extracellular matrix that includes various macromolecules, most importantly proteoglycans and collagen. The cartilage facilitates joint function and protects the underlying subchondral bone by distributing large loads, maintaining low contact stresses, and reducing friction at the joint.

Synovial fluid is formed through a serum ultrafiltration process by cells that form the synovial membrane



(synoviocytes). Synovial cells also manufacture hyaluronic acid (HA, also known as hyaluronate), a glycosaminoglycan that is the major noncellular component of synovial fluid. Synovial fluid supplies nutrients to the avascular articular cartilage; it also provides the viscosity needed to absorb shock from slow movements, as well as the elasticity required to absorb shock from rapid movements.[2]



In early osteoarthritis, swelling of the cartilage usually occurs, because of the increased synthesis of proteoglycans; this reflects an effort by the chondrocytes to repair cartilage damage. This stage may last for years or decades and is characterized by hypertrophic repair of the articular cartilage. As osteoarthritis progresses, the level of proteoglycans eventually drops very low, causing the cartilage to soften and lose elasticity thereby further compromising joint surface integrity. Microscopically, flaking and fibrillations (vertical clefts) develop along the normally smooth articular cartilage on the surface of an osteoarthritic joint. Over time, the loss of cartilage results in loss of joint space.

Erosion of the damaged cartilage in an osteoarthritic joint progresses until the underlying bone is exposed. Bone denuded of its protective cartilage continues to articulate with the opposing surface. Eventually, the increasing stresses exceed the biomechanical yield strength of the bone. The subchondral bone responds with vascular invasion and increased cellularity, becoming thickened and dense (a process known as eburnation) at areas of pressure.[3]

DIAGNOSIS

Osteoarthritis is usually diagnosed based symptoms and the physical signs of the joints. It includes:[4]

- tenderness over the joint
- creaking or grating of the joint (crepitus)
- bony swelling
- excess fluid
- restricted movement
- joint instability
- thinning of the muscles that support the joint.

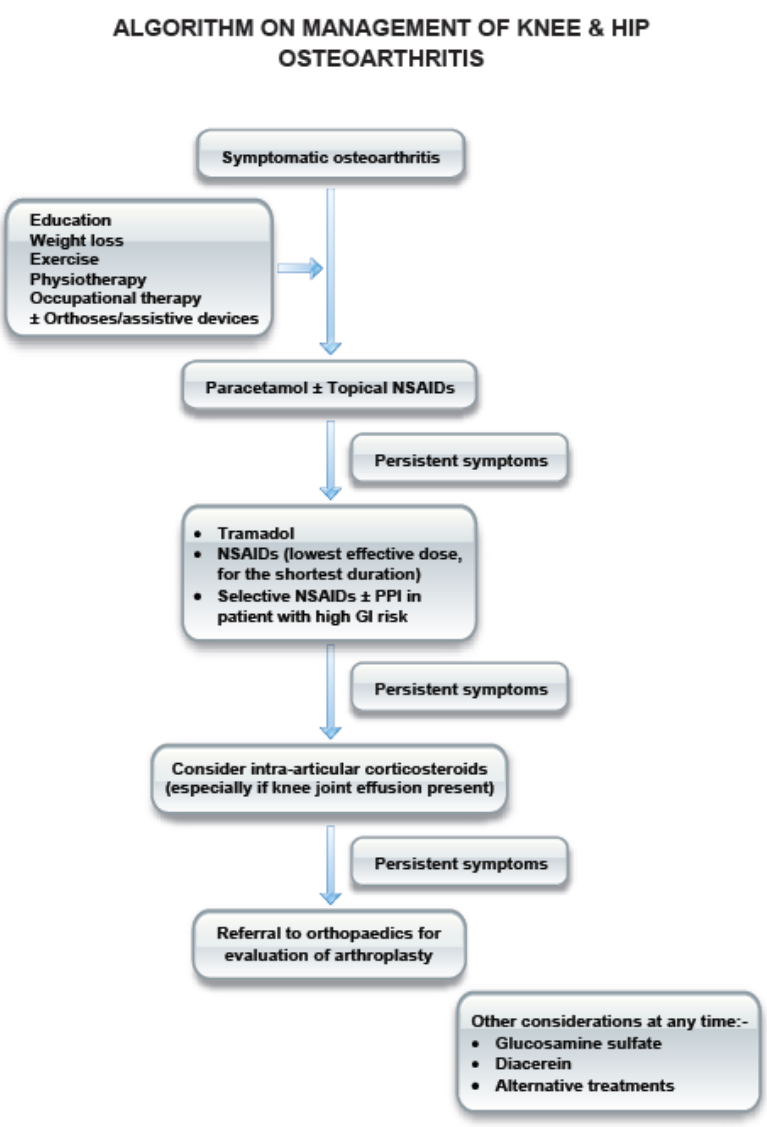
Osteoarthritis is typically diagnosed on the basis of clinical and radiographic evidence. No specific laboratory abnormalities are associated with osteoarthritis.

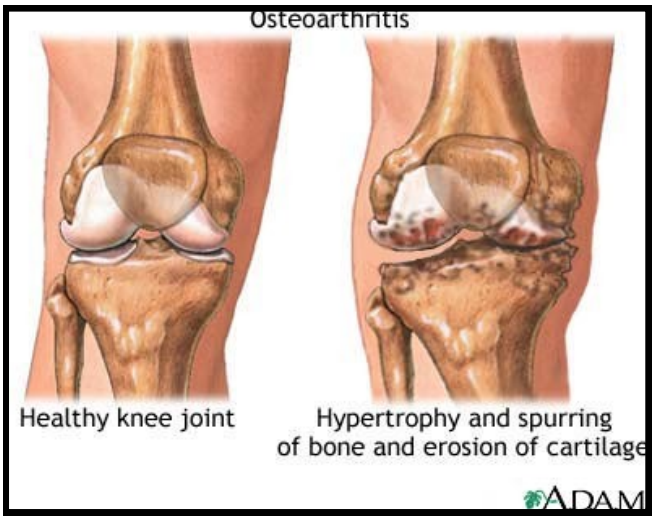
Imaging studies

Plain radiography
Computed tomography (CT) scanning
Magnetic resonance imaging (MRI)
Ultrasonography
Bone scanning

Arthrocentesis

The presence of noninflammatory joint fluid helps distinguish osteoarthritis from other causes of joint pain. Other synovial fluid findings that aid in the differentiation of osteoarthritis from other conditions are negative Gram stains and cultures, as well as the absence of crystals when fluid is viewed under a polarized microscope.[2]





NON-PHARMACOTHERAPY MANAGEMENT

1) Patient education plays an important role in osteoarthritis management.
2) Lifestyle modification:
   a. Weight reduction should be emphasized in the management of patients with knee osteoarthritis and who are overweight
   b. Individualized exercise is effective in reducing pain in hip and knee OA and the intensity as well as the duration of exercise should increase over time. E.g. quadriceps strengthening exercise and knee strengthening exercise.
3) Physiotherapy can relieve pain and improve physical capacity by increasing muscle strength, balance, coordination and joint mobility.
4) Early occupational therapy may result in pain relief and improvement in activities of daily living.
5) Orthoses placed in walking shoes may help in both knee and hip osteoarthritis.[5]

Quadriceps strengthening exercise

Figure A

Lie flat in bed with your legs straight. Bend your ankles and push the back of your knees down firmly against the bed. Hold for five seconds, then return to the original position and relax.

Figure B

Sit on a firm flat surface with one leg bend and keep the other leg straight. Bend your ankle and push the back of your knees down firmly against the bed. Hold for five seconds, then return to the original position and relax.

Figure C

Lie flat in bed with a rolled towel/small cushion under your knee. Bend your ankle and push the back of your knee down firmly against the rolled towel/small cushion (keep knee on the towel/cushion). Hold for five seconds, then return to the original position and relax.

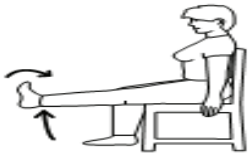


Figure D

Sit on a chair. Straighten your knee and bend your ankle. Hold for five seconds, then return to the original position and relax.

Hip Strengthening exercise

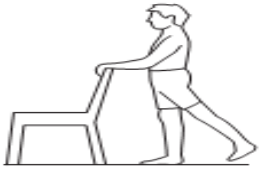


Figure A

Stand straight holding to a chair. Bring your leg backwards, keeping your knee straight (do not lean forwards). Hold for five seconds, then return to the original position and relax.

Figure B

Lie on your back with both knees bent. Then, lift your hips up and straighten one leg while shifting the weight over to the bent leg. Hold for five seconds, then return to the original position and relax.

Figure C

Lie on your back with knees bent. Squeeze your buttocks together and lift your bottom off the floor. Hold for five seconds, then return to the original position and relax.

Figure D

Lie face down. Lift one leg up while keeping the other leg straight on the floor. Hold for five seconds, then return to the original position and relax.

PHARMACOTHERAPY MANAGEMENT

1. <u>Oral therapy</u>

a. Simple analgesics - paracetamol
b. Analgesics with anti-inflammatory properties - Non-steroidal Anti-inflammatory Drugs (NSAIDs)
c. Weak opioid analgesics - tramadol
d. Nutraceutical - glucosamine, chondroitin, diacerein

Paracetamol should be used as first-line analgesic in mild to moderate pain.[5]

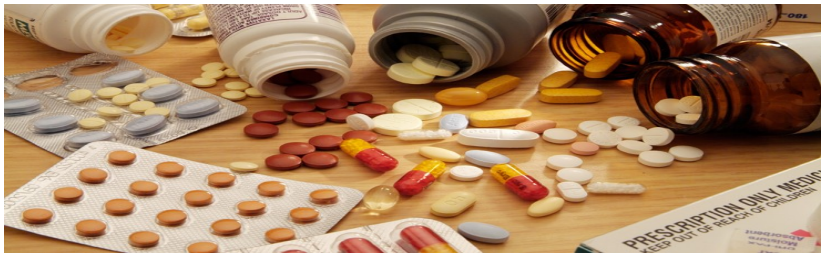
NSAIDs

NSAIDs and COX-2 inhibitors reduce production of prostaglandin by inhibiting the enzyme cyclo-oxygenase. They vary in their selectivity for inhibiting different types of cyclo-oxygenase. They are a class of drugs that provide analgesic and anti-pyretic effects and in higher doses, anti-inflammatory effects. COX-2 inhibitors selectively inhibit COX-2 and thus improve gastro-intestinal tolerance.[5]

Combination therapy with more than one NSAID/COX-2 inhibitor should never be used. There is no benefit in combination therapy and the incidence of side effects may be additive. Caution is required when prescribing NSAIDs in the elderly and those with hypertension, cardiovascular disease, renal or hepatic impairment. Those who are allergic to one NSAID may also be allergic to others. [5]

OPIOD ANALGESICS

Tramadol is a synthetic opioid analgesic. In patients already on NSAIDs for at least 30 days, addition of tramadol/paracetamol combination tablets for 10 days duration is significantly efficacious in managing painful OA compared to those on placebo. Tramadol in all formulations show no major or significant adverse events. Common side effects are dizziness, nausea, vomiting, constipation and drowsiness. This medication has to be used with caution in the elderly.[5]



GLUCOSAMINE & CHONDROITIN

Glucosamine is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids, including glycosaminoglycans (GAG) which is a component of cartilage. Glucosamine sulfate 1500mg/day can be used for pain relief with evaluation at three months after initiation of treatment.[5]

Chondroitin sulfate is a sulfated GAG which is usually found attached to proteins as part of a proteoglycan. It may be beneficial for symptomatic relief in hand OA.[5]

Glucosamine or chondroitin sulfate is required in the synthesis of the GAG component of cartilage, which provides the rationale for oral supplementation of these compounds in OA. The glucosamine and chondroitin preparations available in Malaysia are in various combinations, strengths and purities which may affect their efficacy.[5]

DIACEREIN

Diacerein, a purified anthraquinone derivative, is a drug which inhibits production of interleukin (IL)-1beta, the major proinflammatory cytokine involved in articular cartilage destruction. Thus it may be used for treatment as it provide pain relief.[8]

2. Intra-articular (IA) treatment

a. Corticosteroid. Systemic corticosteroid have no place in OA management. IA corticosteroid may be used for short-term pain relief in acute exacerbation of knee OA but not for the treatment of OA. Triamcinolone hexacetonide appears to be more effective than betamethasone (MOHM, 2013).

b. Viscosupplementation. Hyaluronic acid (HA) is a naturally occurring polysaccharide in the synovial fluid and is responsible for the elasticity and viscosity of synovial fluid. The quantity of HA in the synovial fluid is reduced in the patients who have OA. Thus, HA is devised for intra-articular injection to improve biomechanical function. There are now several different formulations of viscosupplements (hyaluronan and hylan) available. However, there is still lack of supporting evidence of viscosupplementation use in OA treatment.[5]

3. Topical treatment

a. Commonly used topical treatment includes NSAIDs, capsaicin and methylsalicylate in the form of gels, creams and transdermal patches. It may be used as an adjunct in mild to moderate pain.[5]

SUGGESTED MEDICATION DOSAGES AND SIDE EFFECTS

Drug Class	Drug	Recommended Dosages	Side effects	Caution and Contraindications	Comments
Simple analgesic	Paracetamol	0.5 – 1gm, 6 – 8-hourly Max: 4gm/day	Rare	Hepatic impairment, alcohol dependence	Preferred drug particularly in elderly patients Liver damage following overdosage
Non-selective NSAIDs	Ibuprofen	400 – 800 mg, 6 – 8-hourly Max: 3200 mg/day	Peptic ulcer GI bleed Platelet dysfunction Renal impairment Hypertension Allergic reaction in susceptible individuals Increase in CVS events	Gastroduodenal ulcer Asthma Bleeding disorder Renal dysfunction Ischaemic heart disease Cerebrovascular disease Inflammatory bowel disease	Current data suggest that increased CV risk may be an effect of the NSAID/coxib class Physicians and patients should weigh the benefits and risks of NSAID/coxib therapy
	Mefenemic Acid	250 – 500 mg, 6 – 8-hourly Max: 1500 mg/day			
	Diclofenac sodium	50 – 150 mg daily, 8 – 12 hourly Max: 150 mg/day			
	Meloxicam	7.5 – 15 mg daily Max: 15 mg/day			
	Naproxen	250 – 500 mg, 12-hourly Max: 1500 mg/day			
	Naproxen sodium	275- 550 mg, 12 hourly Max: 1650mg/day			
	Piroxicam	10 – 20 mg daily, in single or divided doses Max: 20 mg/day			
Selective COX -2 inhibitors	Celecoxib	200 mg daily Max: 200 mg/day	Renal impairment Allergic reaction in susceptible individuals Increase in CVS events	Ischaemic heart disease Cerebrovascular disease Contraindicated in hypersensitivity to 37learance37des	Associated with a lower risk of serious upper gastrointestinal side effects Current data suggest that increased CV risk may be an effect of the NSAID/coxib class
	Etoricoxib	60 mg daily Max: 90 mg/day	Hypertension Renal impairment Increase in CVS events	Uncontrolled hypertension Ischaemic heart disease Cerebrovascular disease	Physicians and patients should weigh the benefits and risks of NSAID/coxib therapy
Weak opioid	Tramadol	50 – 100 mg, 6 – 8-hourly Max: 400 mg/day	Dizziness Nausea Vomiting Constipation Drowsiness	Risk of seizures in patients with history of seizures and with high doses In elderly, start at lowest dose (50 mg) and maximum of 300 mg daily	Interaction with TCA, SSRI and SNRI
Combination of opioid and paracetamol	Paracetamol 325 mg + tramadol 37.5 mg (Ultracet®)	1 – 2 tablets, 6 – 8-hourly Max: 8 tablets/day	Nausea Vomiting Drowsiness	Hepatic impairment Renal impairment Alcohol dependence Epilepsy	

Nutraceuticals

Drug	Recommended Dosages	Side effects	Caution and Contraindications	Comments
Glucosamine sulfate	1500 mg in single or 3 divided doses Max 1500 mg/day	Nausea Dyspepsia Heartburn Vomiting Constipation Diarrhoea Headache	Hypersensitivity to glucosamine or any of its components Use with caution for patients with an allergy to shellfish and shellfish products Asthmatic patients may be at risk for an asthma exacerbation when taking the combination of glucosamine and chondroitin	

Drug	Recommended Dosages	Side effects	Caution and Contraindications	Comments
Chondroitin sulfate	200 – 400 mg, 8 – 12 hourly Max 1200 mg	Dyspepsia Nausea Vomiting	Asthmatic patients may be at risk for an asthma exacerbation when taking chondroitin Contraindicated in patients with prostate cancer or are at high risk for developing prostate cancer Caution in diabetics as chondroitin affects glucose level	
Diacerein	50 mg 12-hourly	Diarrhoea Epigastric pain Nausea Vomiting Intense yellow colouring of urine Skin reactions	Hypersensitivity to anthraquinone derivatives Inflammatory organic bowel disease (ulcerative colitis, Crohn's disease) Intestinal obstruction or partial obstruction, Severe liver failure Rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption due to presence of lactose.	Creatinine 39learance (ml/min) <30 Dosage Recommendation 25 mg daily Antacid use may decrease diacerein absorption, so it is advised to take antacids within an interval of two hours
Avocado soybean unsaponifiables	300 mg daily	Diarrhea Epigastric pain Extremely rare cases of liver disorders including increased transaminases, alkaline phosphatases, bilirubin and gamma-glutamyl transpeptidase	Previous history of allergic reaction to any of the ingredients	Infrequent lipid-scented regurgitations which may be avoided by taking the capsule during a meal.

PRIMARY PREVENTION

Identifying and modifying the risk factors can help in preventing OA and its progression. Many of these risk factors are of particular importance in weight-bearing joints. Prevention of obesity, weight reduction in the obese and health education pertaining to joint protection techniques including avoidance of trauma to the joints are recommended as measures for primary prevention. Currently, there is no evidence available to recommend the intake of any medication to prevent OA. An important aspect of primary prevention is to identify those individuals at risk.5

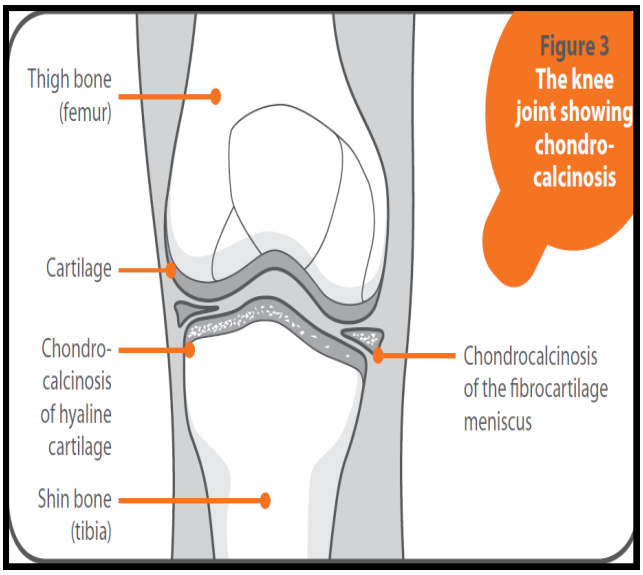
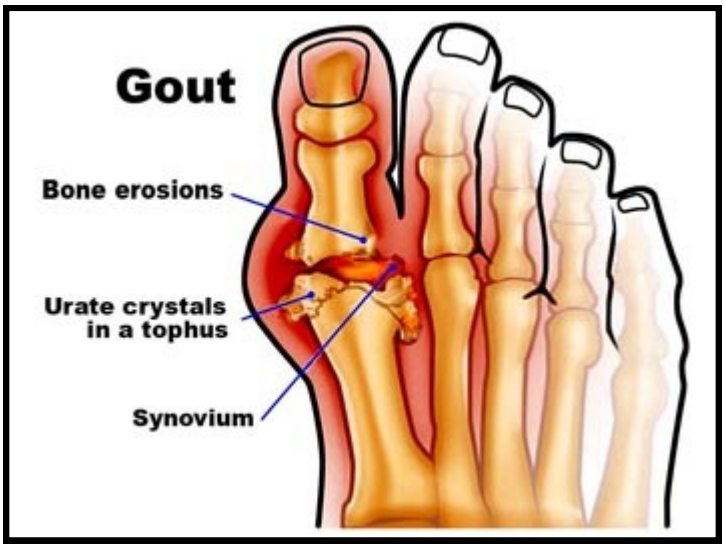


Figure 3 The knee joint showing chondro-calcinosis



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9. Arthritis Research UK Calcium crystal disease

Risperidone and Paliperidone: Risk of Intraoperative Floppy Iris Syndrome (IFIS)

Background

The atypical antipsychotics, risperidone and paliperidone, have been associated with an increased risk of intraoperative floppy iris syndrome (IFIS) in patients undergoing cataract surgery. IFIS is an intraoperative complication of cataract surgery first reported in 2005 in relation to the use of tamsulosin. Other drugs that have been linked to IFIS include alfuzosin, doxazosin and labetolol. Inhibition of α1-adrenergic receptors in the iris dilator muscle causes relaxation of this muscle, leading to a floppy iris and miosis. IFIS may increase the risk of **complications** during and after surgery. Diagnosis involves the combined presence of **three clinical signs,** as listed below:

a) billowing of flaccid iris stroma during normal irrigation and aspiration
b) progressive pupil constriction during the surgery
c) tendency for the iris to prolapse towards the phaco and side port incisions during surgery

Local scenario

Risperidone was first registered in Malaysia in 1996, and paliperidone in 2008. Both are approved for the treatment of schizophrenia *(please refer to the product inserts for full prescribing information)*. Currently, there are 36 approved products containing risperidone and 9 containing paliperidone locally. A circular has been issued by NPCB for all the package inserts to be updated with this safety information.

Adverse Drug Reaction Reports

The NPCB Drug Safety Monitoring Centre has received **391 reports** related to **risperidone** of which none reported IFIS specifically or any ADR occurring during cataract surgery. There were eight (8) reports involving vision disorders, namely vision blurred (5), scleral discolouration, mydriasis and eye discharge. The **most frequently** reported adverse events were tremor (32), extrapyramidal disorder (31), and akathisia (26).
There were **81 reports** related to **paliperidone**, none involving IFIS or ADRs related to cataract surgery. One report of blurred vision was received. The **most frequently** reported adverse events were extrapyramidal disorder, medicine ineffective, marked restlessness, and schizophrenia aggravated (6 events each).

Advice for Healthcare Professionals

- Patients must be asked about **current or prior use** of risperidone- or paliperidone-containing products when taking a medication history before cataract surgery.
- In patients with such medication history, the surgery should be approached with **caution**.
- All ADRs suspected to be related to risperidone or paliperidone should be reported to the NPCB.

Mencevax ACWY® Vaccine: New Data on Antibody Persistence

Background

Mencevax ACWY® is a **quadrivalent polysaccharide meningococcal vaccine** (serogroups A, C, W-135 and Y). It is indicated for active immunisation against meningococcal disease, especially for those at **high risk**, including travellers to endemic areas, asplenic patients, those living in closed communities and close contacts of patients with the disease. A Direct Healthcare Professional Communication (DHPC) was issued recently regarding new data that suggest immunity offered by Mencevax ACWY® may **not persist for up to 3 years**, as previously stated in the product insert. New data on antibody persistence showed that immunity to serogroups W-135 and Y in individuals aged 11-55 years decreased to 24% and 44% respectively **two years** after vaccination. There was also waning of serum bactericidal antibody titre against serogroup A **one year** post-vaccination.

Local scenario

Mencevax ACWY® has been registered in Malaysia since 2008. It is normally used for **short-term protection** and is offered by the Ministry of Health for vaccination of pilgrims travelling to Mecca. The meningococcal A,C,Y,W-135 vaccine is listed in the Ministry of Health Drug Formulary under **category B** (may be prescribed by medical officers and specialists).

Advice for Healthcare Professionals

- Individuals remaining at high risk of exposure to meningococcal serogroups A, W-135 and Y should be **considered for revaccination** according to local recommendations.
- Use of **conjugate vaccines** is recommended for revaccination within two years of previous Mencevax ACWY® dose.
- Please **report** all suspected adverse drug reactions related to meningococcal vaccines to the NPCB.

GOODBYE TO

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