Evidence-based Pharmacy Practice (EBPP):

ARTHRITIS

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The most common types of arthritis are osteoarthritis (OA), inflammatory arthritis (especially rheumatoid arthritis (RA)) and gout. This article will focus on osteoarthritis and rheumatoid arthritis. A brief overview of the different forms of arthritis is given in Table 1.

Figure 1 illustrates the basic difference between osteoarthritis (where the cartilage is involved) and rheumatoid arthritis (synovial membrane involvement). Osteoarthritis is a deterioration of cartilage and overgrowth of bone often due to "wear and tear". Rheumatoid arthritis is the inflammation of a joint's connective tissues, such as the synovial membranes, which leads to the destruction of the articular cartilage.

EPIDEMIOLOGY OF ARTHRITIS

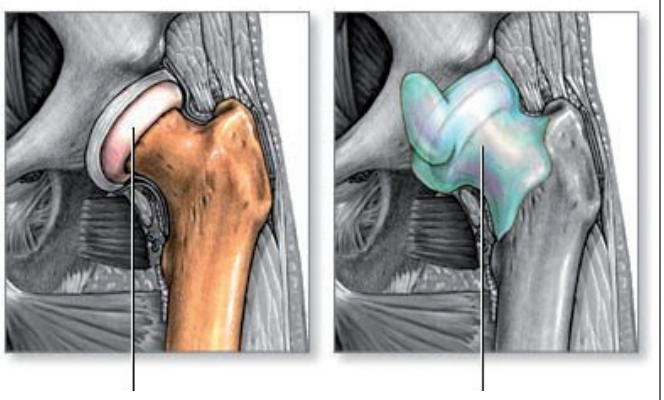
Arthritis affects approximately 10% of the adult population in the United Kingdom.[1] *Osteoarthritis* is the most common joint disorder[1,2] and can affect as many as 10% to 20% of people over the age of 64 years.[1] It often becomes symptomatic in the 40s and 50s and is nearly universal by the age of 80 years.[2] Below 40 years, most cases of osteoarthritis occur in men and result from trauma.[2] Women predominate from age 40 to 70 years, after which men and women are equally affected.[2] The high prevalence of osteoarthritis makes it the most common cause of arthritic disability in the population, with chronic pain, social isolation and depression contributing to reduced quality of life. The burden of osteoarthritis management falls largely within primary health care services.

The *inflammatory arthritic conditions* tend to be diagnosed earlier and affect about one to two percent of the population.[1] *Rheumatoid arthritis* affects about one percent of the population.[2] Women are affected two to three times more often than men.[2] Onset may be at any age, most often between 35 and 50 years.[2] Rheumatoid arthritis often impacts severely on quality of life and it is estimated that 40% of people with rheumatoid arthritis stop working within five years of diagnosis.[3]

Table 1: Forms of arthritis[1]

Diagnosis	Cinical definition
Osteoarthritis	Degenerative damage and loss of articular cartilage, especially in the weight bearing joints and hypertrophy in the subchondral (to which the joint is attached) bone
Rheumatoid arthritis	Chronic systemic inflammatory disease characterised by potentially deforming symmetrical polyarthritis and extra-articular features
Juvenile arthritis	Inflammatory joint disease with chronic synovitis in children in whom the onset of disease occurred before the age of 16 years
Psoriatic arthritis	Peripheral inflammatory polyarthritis with presence of psoriasis without rheumatoid nodules
Ankylosing spondylitis	Progressive chronic, systemic inflammatory rheumatic disease with involvement of sacroiliac joints and spine, absence of microbial infection and various extra-cellular manifestations
Gout	Abnormality of urate metabolism resulting in deposition of monosodium urate monohydrate crystals in the synovial fluid, soft tissue and urinary tract, causing an inflammatory response

Figure 1: Osteoarthritis versus rheumatoid arthritis



OSTEOARTHRITIS

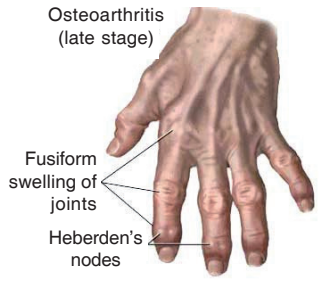
Osteoarthritis (OA) is a non-inflammatory disease of the joints which is characterised by degeneration of the cartilage of the joints and a hardening (sclerosis) of the underlying bone.[4] Osteoarthritis is a joint "wearing out" or the "wear and tear" of a specific joint (usually large joints). It is a degenerative disease primarily of weight-bearing joints (commonly the spine, hip, knee and also the terminal interphalangeal joints of the hands, but any joint may be involved). It has an asymmetrical distribution.

Signs and symptoms[4]

- Osteoarthritis presents with joint pain on movement and deep, boring pain at night, deformity from bone overgrowth at articular margins and effusion with damaged joints. Exercise and movement may make the joint pain worse.
- Passing stiffness after rest (usually of short duration).
- Restricted mobility of the joints.
- The joints appear larger and wider than usual.
- Sometimes soft tissue swelling and sensitivity to pressure is present as inflammation or an effusion around the joint.
- Crepitus (cracking of the joints) with movement. Pain becomes more severe under certain weather conditions (for example, cold, humidity and low barometric pressure).
- Flare-ups and temporary improvements alternate, but the condition generally worsens with the passage of time.

Figure 2 shows osteoarthritis with involvement of the distal interphalangeal joints with Heberden's nodes. Heberden's nodes are bony nodules (osteophytes) at the terminal finger joints. Osteoarthritis is most commonly seen in the elderly, who may present with nodules around the terminal inter-phalangeal joints. Hallux valgus is a marked osteoarthritic deformity of the metatarsophalangeal joint of the big toe.

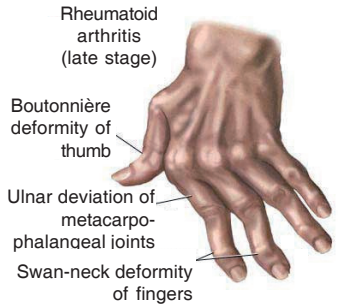
Figure 2: Osteoarthritis



RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) (inflammatory arthritis, a polyarthritis) is a chronic generalised autoimmune, connective tissue disorder, with joint disease as the prominent feature. It is part of a generalised disease involving various organs, including the joints, tendons and bursae. The joints are often symmetrically involved, especially the wrists, fingers and other synovial joints (for example, knees and elbows) with stiffness and pain on movement, and fixed deformity (for example, ulnar deviation of wrist and fingers) if chronic. Affliction of the joints begins in small peripheral joints and spreads slowly to the larger joints. In the case of the hands, it is characteristic that the metacarpophalangeal and proximal interphalangeal joints are affected. Larger joints include the vertebrae, the knees and the ankles. Rheumatoid nodules on the extensor surface of the elbows may be visible. See Figure 3 for an illustration of rheumatoid arthritis with ulnar deviation of the metacarpophalangeal joints, Boutonnière deformity and Swan-neck deformity.

Figure 3: Rheumatoid arthritis



Signs and symptoms[4]

- General clinical features include fever and intermittent or chronic ill health.
- Swelling and sensitivity of the joints. Joints are inflamed if the arthritis is active.
- Stiffness of the joints occurs especially in the morning, and improves with movement during the course of the day. Stiffness is worse after rest (for example, on waking) and improves with use.
- Pain in joints and tendons is exacerbated by movement.
- Deformities, instability and dislocations can occur in the advanced stages and movements become seriously inhibited.
- Muscle wasting often happens due to disuse atrophy.
- Organs particularly involved are the eyes and the skin.

Other clinical features, apart from fever and joint disease, include[5]:

- *Periarticular*: Soft tissue swelling and inflammation, tenosynovitis (for example, Achilles tendinitis).
- *Skin*: Rash, subcutaneous nodules at elbow.
- *Lung*: Infiltration causing restrictive lung disease (nodules on X-ray).
- *Pericarditis*.
- *Vasculitis*: Splinter haemorrhages at nailbed.
- *Neuropathy*: Peripheral, usually sensory.
- *Reticuloendothelial system*: Spleen and lymph node enlargement.
- *Eyes*: Keratoconjunctivitis sicca (dry eye syndrome).
- *Sjögren's syndrome* is the combination of rheumatoid arthritis with dry eyes and dry mouth (xerostomia) due to lacrimal and salivary gland infiltration.

In severe, long-standing, rheumatoid disease (and also disabling neurological disease), disability may be severe and is classified into four grades[5]:

- *Complete independence*: No support needed.
- *Independent with support*: Such as adapted and special appliances at work and home.
- *Partially dependent*: Requiring assistance for complex movement such as bathing and dressing.

- *Totally dependent*: Being confined to a wheelchair or bed.

AETIOLOGY/PATHOPHYSIOLOGY OF ARTHRITIS

There are innumerable causes of arthritis (painful, swollen, tender joints) and arthralgia (painful joints).[6] A brief summary of osteoarthritis and rheumatoid arthritis is given.

Osteoarthritis

Pre-disposing factors include[4,5]:

- *Age*: Normal aging of the joints can ultimately lead to osteoarthritis or joint failure. Radiological evidence of osteoarthritis is present in 98% of people over the age of 60 years (not all of them display symptoms). Osteoarthritis is common in the elderly or after trauma to a joint.
- *Obesity*.
- *Injuries* to the joints speed up the aging process and can lead to osteoarthritis at any age. Injuries can result from the following:
  - Trauma (jogging spines, sportsmen's knees or surgery).
  - Career: People in jobs where they pick up and carry heavy objects are predisposed.
  - Postural abnormalities, for example a person with one leg shorter than the other or a weakened bone.
- There is a *familial tendency*.
- People who lead *less active lives* are more inclined to develop the condition.

Rheumatoid arthritis

The precise cause of rheumatoid arthritis is unknown.[8] A genetic predisposition has been identified. Environmental factors (for example, viral infections) may play a role as well as cigarette smoking.[8]

DIAGNOSIS

Osteoarthritis

The cartilage becomes irregular early in the disease, and later extensive destruction of the cartilage occurs. The underlying bone is inactive and sclerotic, but may present with areas of osteoporosis. There is also bony remodelling of the joint with the formation of bony protrusions (osteophytes) laterally to the joints. Occasional synovitis or an effusion of the joint may occur. Characteristically, certain joints are more seriously affected than others. X-rays will typically show loss of joint space (that is, loss of cartilage), osteophytes at joint margins, bone cysts and sclerosis at articular surfaces.

Rheumatoid arthritis

Rheumatoid arthritis is usually symmetrical. It predominantly affects the hands, causing swelling of the proximal finger joints and ulnar deviation of the fingers, and also the wrists, with muscle wasting around affected joints. Rheumatoid nodules may be present over the lower ulnar at the elbows. There is no single diagnostic test for rheumatoid arthritis.[3] It is diagnosed by considering the following[3]:

- Normochromic, normocytic anaemia.
- Raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).
- Positive rheumatoid factor (circulating immunoglobulin M (IgM) against patient's own IgG) in 80% of cases. In seronegative arthritis (for example, psoriatic arthritis, ankylosing spondylitis and Reiter's disease) the rheumatoid factor is absent.

Diagnosis, however, relies heavily on history taking and clinical examination and less on investigations.[3] The useful investigations include CRP, ESR, a full blood count, liver function tests, urinanalysis, antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibody (anti-CCP) and radiology.

Furthermore, the skin should be examined for:

- Tophi of gout found around joints and on the cartilage of the ears.
- Subcutaneous nodules at the elbow in rheumatoid arthritis.
- Tight skin and/or superficial calcification of the fingers in scleroderma.
- Thimble pitting of nails and psoriasis, usually at the elbow, in psoriatic arthritis.
- Red or brown nailfold infarcts due to vasculitis in rheumatoid arthritis.
- Superficial redness over an infected or gouty joint.

The eyes should be examined for:

- Dryness (and dry mouth from decreased saliva) in Sjögren's disease.
- Conjunctivitis of Reiter's disease.
- Iritis of ankylosing spondylitis.
- Scleritis of rheumatoid arthritis.

Infective (septic) arthritis

Septic infected arthritis must be considered in the diagnosis of an acutely inflamed joint. Acute onset of pain in a single joint with severe swelling, redness, sensitivity and inhibition of movement is indicative of septic arthritis. Systemic symptoms such as fever and malaise occur in most patients. Patients with infective arthritis must urgently be referred to a medical practitioner on the same day.

COUNSELLING APPROACH TO FOLLOW

A thorough medical and drug history should be taken to enable the pharmacist to rule out serious pathology. A number of specific questions should be asked of the patient (see Table 2). Pharmacists should only treat conditions of the joints caused by *osteoarthritis*, gout or trauma. The goals of therapy for osteoarthritis are to relieve symptoms, to maintain or improve mobility, to minimise functional disability and improve physical functioning, and to educate patients and caregivers to assist patients to understand their condi-

tion and make informed decisions about which therapies to choose. The goals in the treatment of *rheumatoid arthritis* are similar, but also include to slow disease progression and to achieve remission. Rheumatoid arthritis should be referred to a medical practitioner, with the pharmacist only providing temporary treatment (for example, for pain).[4]

WHEN TO REFER

Trigger points indicative of referral, which may indicate a serious condition[4]:

- Pain that inhibits movement and is becoming progressively worse. Also pain which spreads to the buttocks, legs, knees and/or groin.
- Swelling that is spreading, or if oedema is present. Pitting oedema of the ankle may indicate deep vein thrombosis.
- Sensitivity to pressure. A typical patient with a fracture, dislocation or total rupture of a muscle or ligament will be distressed by, and will refuse, any contact.
- Any instability or severe deformity of a joint (this may indicate dislocation).
- Associated muscle weakness of the legs and feet (for example, a drop foot).
- Loss of sensation in the legs.
- Associated signs and symptoms which may indicate a serious, chronic or systemic disease include fever, pallor (anaemia), weight loss, headache or skin rash.
- More extensive pathology, for example multiple afflictions of the joints and widespread muscular pain.
- Associated disease conditions such as obesity, previous surgery to the affected joint or muscle, and paralysis of the limbs.
- Any sign or symptoms of nerve damage (for example, muscle weakness or paralysis, diminution or loss of sensation, or paraesthesia (pins and needles, tingling sensation).
- Pain that progressively worsens as the patient walks and improves as he or she bends (indicates a spinal stenosis).

Table 2: Specific questions to ask the patient with arthritis

Factor	Question
Presence and nature of pain	• Describe the pain? • Where is the pain? • How long has the pain been present? • Is the pain acute or chronic? • What is the pattern of joint involvement and pain?
Demographics of patient	• How old are you? (this can assist with the differential diagnosis) • What type of work do you do/have you done previously? • Is there a family history of joint disease?
Symptoms and associated symptoms	• Are the symptoms localised? • Are the symptoms symmetrical or only on one side? • Is there swelling or deformity? • Is there associated stiffness, tenderness, swelling, tingling, instability or a dead feeling? • Are there any systemic symptoms (malaise or fever)? • Is the condition inflammatory or non-inflammatory?
Onset	• When did it start? • How did it start? • Have you injured the joint (trauma)? Recently or previously?
Movement	• How far can you walk? • Can you walk upstairs? • Is any particular movement difficult? • Can you dress yourself (if yes, how long does it take)?
Periodicity	• Is it worse at certain times? • Is it exacerbated by movement?

TREATMENT OPTIONS FOR ARTHRITIS

Therapeutic objectives

For most patients management of arthritis relies on optimising the use of pharmacotherapy. Long-term outcomes rely on an integration of drug treatment with exercise, lifestyle adjustment and physiotherapy.[1] Pharmaceutical care is therefore central to the treatment of patients with arthritis.[1]

General measures

Diet is an important aspect in the management of arthritis, but the so-called "dietary cures" are controversial.[1] The most important non-pharmacological measures are summarised below.

Osteoarthritis

The following precautionary measures can assist in relieving the condition[2,7,8]:

- *Weight and trauma reduction*. Obesity increases the strain on weight-bearing joints, such as the hips and knees. Weight reduction can reduce pain and improve mobility.
- The application of *warm, moist heat and slow massage* of the affected joints.
- A reduction (but not the total absence) of normal activity. Normal activity can prevent further loss of cartilage.
- *Walking sticks and other aids* may reduce symptoms by reducing the weight on the joints.
- Patients should be encouraged to eat a *healthy, balanced diet*, eating fatty and sugary foods in moderation.
- *Glucosamine* may improve symptoms of osteoarthritis, but evidence is limited.
- *Antioxidants and vitamin D*. There is some evidence that an increased intake of antioxidants (vitamins C and E and selenium) and vitamin D may reduce the progression of osteoarthritis.
- *Fish oils*. There is anecdotal evidence that fish oils are useful in osteoarthritis but there is more evidence of its benefit in rheumatoid arthritis.

Rheumatoid arthritis

Useful non-pharmacological measures include[2,7,8]:

- *Exercise* specifically designed to maintain muscle strength and joint mobility. Physiotherapy may be beneficial.
- *Rest* when the joints are swollen, warm to the touch and painful.
- *Education* of the patient and family regarding the full impact of rheumatoid arthritis on their lives.
- *Splints and other orthopaedic devices* may be employed to reduce movement of an inflamed joint.
- *Body weight.* Obesity should be corrected by encouraging a healthy, balanced diet.
- *Food allergy* has been suggested as a cause of rheumatoid arthritis and the popular literature advocates exclusion diets to identify possible dietary causes. Exclusion diets may, however, lead to nutritional deficiencies.
- *Fish oils* contain omega-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexanoic acid), which may reduce symptoms of pain, morning stiffness and swollen joints. They appear to reduce production of pro-inflammatory prostaglandins and leukotrienes. Fish oils can be obtained from oily fish (for example, mackerel, herring and sardines) but to obtain beneficial amounts of fatty acids supplements are a more manageable alternative.
- *Evening primrose oil and starflower oil* contain gamma-linolenic acid (GLA), which is necessary for the production of PGE_1. Increased intake of GLA may increase the production of PGE_1 and this may assist with relieving pain and stiffness. There is, however, no clear proof of clinical benefit.

Pharmacological treatment

Osteoarthritis

There is no specific treatment for osteoarthritis. There is also no evidence to suggest that medicines have a significant influence on the natural history of osteoarthritis.[9] In general, pharmacological treatment involves analgesia with aspirin, paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs). Pain relief in osteoarthritis starts with simple oral analgesics (such as paracetamol), which can be given in combination with opioid or non-opioid analgesics if necessary. NSAIDs such as ibuprofen should be considered as alternatives or adjuncts for pain relief in those who do not respond adequately to simple analgesics.

Topical treatment involves the use of anti-inflammatory preparations (for example, indomethacin, sodium diclofenac and flufenamic acid) for pain localised to specific joints, although their effectiveness is limited.[1]

Patients taking NSAIDs have a three-to-five fold increased risk of gastrointestinal (GI) complications compared with non-users. Misoprostol or proton pump inhibitors (PPIs) may be prescribed to reduce GI complications but prophylaxis with these agents may not be cost-effective, except in targeted high-risk patients. The cyclo-oxygenase-2 (COX-2) inhibitors may reduce GI complications.

Other treatments include glucosamine, chondroitin, hyaluronic acid and various other agents (for example, capsaicin, methyl salicylate, menthol, diacerein and intra-articular injections of the radioactive isotope Yttrium-90).

Rheumatoid arthritis

Although NSAIDs are effective in ameliorating the symptoms of rheumatoid arthritis, they have no effects on disease progression. Remission or control of inflammatory joint disease requires the use of disease-modifying antirheumatic drugs (DMARDs). Most people with rheumatoid arthritis require DMARD therapy to control and prevent joint damage. Although DMARDs bear little resemblance to each other pharmacologically, they share the following characteristics[8]:

- DMARDs exert little direct anti-inflammatory or analgesic effects. Therefore, they are often used together with NSAIDs.
- The benefit derived from DMARD therapy may take weeks or even months to manifest.
- Approximately two-thirds of patients on DMARDs derive clinical improvement from rheumatoid arthritis symptoms.
- There is frequently an improvement in serological measures of disease activity (ESR, CRP) with DMARD therapy.

DMARD therapy should preferably be initiated by a specialist as early as possible in the disease process. Since the maximal damage occurs within the first two years of the disease and is largely irreversible, early intervention is expected to produce better control and a more favourable outcome.[3,10] See Table 3 for a summary of recommendations about early referral from various rheumatoid arthritis guidelines.

Treatment usually begins with methotrexate and then other

Table 3: Guideline recommendations about early referral in rheumatoid arthritis[3]

Guideline	Recommendation
SIGN 2000	All patients with persistent inflammatory joint disease (more than 6 to 8 weeks duration) already receiving simple analgesics and NSAIDs should be considered for referral for a specialist rheumatology opinion and DMARD therapy, preferably within 12 weeks.
PRODIGY 2005	Rheumatology referral is strongly recommended if symptoms persist for more than 6 weeks, even if there is a response to NSAIDs. Ideally, the person should be seen within 12 weeks of the onset of symptoms.
British Society for Rheumatology (BSR) Standards of Care 2005	The rheumatology department should see all patients with a likely diagnosis of rheumatoid arthritis within 12 weeks of referral, where this is indicated in the general practitioner's referral letter.

DMARDs such as sulphasalazine, oral gold (auranofin), penicillamine and hydroxychloroquine are added when inflammation is not controlled. DMARDs reduce joint inflammation with fairly similar efficacy. Gold has been used in the treatment of rheumatoid arthritis since 1927, but it is slow-acting and often requires up to six months to show its effect.[11] SIGN guidelines recommend sulphasalazine and methotrexate as the DMARDs of choice due to their more favourable efficacy/toxicity profiles.[3] Leflunomide is a newer DMARD which seems to be as effective as methotrexate or sulphasalazine at improving inflammation and function. Its long-term effects are, however, still unclear.[3] All DMARDs are associated with considerable toxicity (especially marrow-related) and some adverse reactions are potentially fatal. DMARDs do not consistently induce remission and their use is associated with adverse effects, causing more than 70% of patients to default from therapy within five years.[10] People prescribed DMARDs therefore require close monitoring for adverse effects and drug interactions.

Assessments by meta-analysis have suggested that methotrexate and hydroxychloroquine have the highest efficacy/toxicity ratio. DMARDs have conventionally been used in patients with radiological evidence of erosive disease, or in rapid functional decline, but they are increasingly being used earlier and more intensely in rheumatoid arthritis. The more widespread use of methotrexate places increasing responsibility on primary care practitioners for patient education and monitoring for dose-related toxicity.

A wider range of agents are now used as DMARDs in the treatment of rheumatoid arthritis. Combination therapy has been studied, but the results are inconclusive.[1] Paracetamol (with codeine, where needed) should preferably be used instead of NSAIDs. If an NSAID is prescribed for a patient with rheumatoid arthritis, the dose should be reduced and if possible, withdrawn when a good response to DMARDs is achieved.[3] Commonly, however, patients with rheumatoid arthritis are given two, three or four DMARDs simultaneously.[10] Emphasis is placed on systematic monitoring of disease progression to signal the need to make changes in the DMARD regimen. The strategy of using changes in treatment regimens to achieve greater individualisation of the treatment course is known as the "saw tooth" strategy. The DMARD "saw tooth" strategy involves the following[1]:

- Use DMARDs early.
- Use one or more DMARDs continuously.
- Monitor disability and other outcomes.
- Set ceilings of acceptable disability in order to define decision points for the need to change treatment.
- Modify treatment systematically, by changing DMARD treatment at each decision point.
- Use analgesic/NSAIDs as adjunctive (symptomatic) treatment only.

A "step down" approach has also been advocated.[1] In such cases, DMARD combinations are first used intensively to achieve "remission" of disease activity and then the more toxic components are gradually withdrawn with the aim of limiting toxicity while maintaining disease control. Corticosteroids and NSAIDs are used as adjunctive agents to provide what has been termed "bridge therapy" while DMARDs take effect.[1]

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Table 4: Evidence-based guidelines for arthritis treatment[1]

Therapeutic intervention	Summary of findings
Simple analgesics/ NSAIDs	In inflammatory arthritis, NSAIDs are more effective than simple analgesics. Differences in efficacy between most NSAIDs are small but responses show high individual patient variation. NSAID-gastrointestinal toxicity is dose related; ibuprofen has the lowest risk of GI complications.
Sulphasalazine	Sulphasalazine is as effective as injectable gold, penicillamine and methotrexate and is significantly better than antimalarials, oral gold and azathioprine. It has a better effect on disease progression than hydroxychloroquine. Triple combinations with a steroid plus methotrexate are more effective than sulphasalazine alone.
Antimalarials (hydroxychloroquine and chloroquine)	Meta-analysis demonstrates a relatively high efficacy to toxicity ratio compared with other DMARDs. Hydroxychloroquine (rather than chloroquine) tends to be used in practice. The combination of chloroquine and methotrexate is more effective than methotrexate alone. Triple therapy with hydroxychloroquine, sulphasalazine and methotrexate is more effective than either hydroxychloroquine/sulphasalazine or methotrexate alone.
Methotrexate	Methotrexate is probably the most effective and most rapidly acting DMARD. Combinations of methotrexate with ciclosporin and with sulphasalazine and hydroxychloroquine show better clinical outcomes than methotrexate alone.
Gold (oral)	Combination with corticosteroids increases effectiveness of oral gold. Oral gold is significantly less effective than methotrexate, sulphasalazine, and penicillamine.
D-Penicillamine	As effective as methotrexate and sulphasalazine. The penicillamine/oral gold combination shows improved outcomes compared with penicillamine alone. However, there is lack of evidence for long-term efficacy and poor long-term tolerance.
Corticosteroids	Meta-analysis of oral prednisolone 2.5 to 12.5 mg/day confirms effectiveness in symptomatic control. Addition of prednisolone 7.5 mg to DMARD regimens shows short-term rather than long-term effects.