BNF CHAPTER 10: MUSCULOSKELETAL & JOINT DISEASES

10.1 DRUGS USED IN RHEUMATIC DISEASES AND GOUT

MANAGEMENT OF OSTEOARTHRITIS: NICE Guideline CG177
See local pathway for osteoarthritis.

SUMMARY OF RECOMMENDATIONS:

A. Pharmacological
- Paracetamol (regular dosing may be required) AND/OR
- Topical non-steroidal anti-inflammatory drugs (NSAIDs) or topical capsaicin for knee or hand osteoarthritis

If above agent(s) are ineffective or insufficient then consider;
- Substitution or addition of an oral NSAID [or COX-2 inhibitor (but NOT etoricoxib)]. See 10.1.1 below for prescribing advice and formulary choices OR
- Opioid analgesics
- Consider intra-articular corticosteroid injections if pain is moderate to severe.

B. Non-pharmacological
- Application of heat or cold to the site of pain.
- Transcutaneous electrical nerve stimulation (TENS).
- Manipulation and stretching, particularly for hip osteoarthritis.
- Assessment for bracing/joint supports/insoles for people with biomechanical joint pain or instability.
- Assistive devices (for example, walking sticks and tap turners) for people with specific problems with daily activities. Expert advice may be required.

C. Treatments not recommended

DO NOT PRESCRIBE: rubefacients
- intra-articular hyaluronan injections
- electro-acupuncture
- chondroitin or glucosamine products
10.1.1 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

NSAIDs have an analgesic, not anti-inflammatory, effect with a potency similar to paracetamol when taken on a ‘when required’ basis. Taken regularly, most NSAIDs will produce a maximal analgesic effect within a week and anti-inflammatory effect in three weeks. There is considerable variation in individual patient response and it may be necessary to try a number of different drugs before finding one to suit a particular patient. Modified-release (MR) preparations are unsuitable for ‘when required’ use, but given at night, may benefit patients suffering from morning stiffness.

The main differences between the NSAIDs are in their potency and side-effect profile. More potent NSAIDs tend to have a higher incidence of adverse effects. All NSAIDs cause gastro-intestinal (GI) irritation regardless of the route of administration since this effect is systemic as well as local. Patients should be advised to take NSAIDs with food, to reduce the risk of direct GI irritation. Consider prescribing a proton pump inhibitor (PPI) for those at particularly high risk of GI adverse effects (e.g., regular persistent use, >65 years, taking warfarin, or other co-morbidity). Care should be exercised when co-prescribing NSAIDs with low dose aspirin, corticosteroids or other GI irritants since this can increase the risk of GI adverse effects.

NSAIDs are potentially toxic agents and, ideally, should be prescribed as a treatment course, rather than a long term therapy.

The following NSAIDs are available for initial treatment of routine inflammatory conditions. Other NSAIDs are available for rheumatoid arthritis patients on the advice of the Consultant Rheumatologist.

### NSAIDs / COX2 inhibitors and associated risks

- NSAIDs, including COX2 inhibitors, are associated with an increased risk of thrombotic events (myocardial infarction (MI) and stroke) and should only be used following a cardiovascular risk assessment for the shortest time necessary and lowest dose possible.

- Naproxen is associated with a lower cardiovascular risk and has not been associated with an increased risk of MI when taken regularly at high dose (500mg bd).

- COX2 inhibitors should only be prescribed to patients with high risk of GI side effects, and co-prescribed with a PPI (e.g., lansoprazole 15mg, omeprazole 20mg).

- For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of NSAIDs / COX2 inhibitors, in particular cardiovascular, gastrointestinal and other risk factors.

- Review the continuing need for NSAIDs / COX2 inhibitors.

- Alternative treatments may include regular paracetamol, or weak opioid analgesics.

- Gastro-protection with a PPI should always be considered, particularly for ‘at risk’ patients (e.g., long term NSAID use, >65 years, taking concomitant GI irritants, or other co-morbidity).

- Remember to discontinue gastro-protection if NSAIDs / COX2 inhibitors are no longer required.
First Line
- **Ibuprofen**
  - 200mg, 400mg tablets
  - 100mg/5mL syrup
Ibuprofen has been reported to be associated with the lowest risk of gastrointestinal adverse reactions especially at doses below 1.2g/24 hours
Doses above 1.6g may be required for an anti-inflammatory effect, up to a maximum of 2.4g daily, given in divided doses however this may increase the cardiovascular risk. Avoid giving with low dose aspirin as the anti-platelet effect of aspirin can be reduced.

- **Naproxen**
  - 250mg, 500mg tablets
  - 125mg/5mL suspension
By mouth, 250 - 500mg twice daily. Naproxen at any dose is associated with a lower thrombotic risk than other NSAIDs.

Second Line (where alternative administration routes are needed)
- **Diclofenac**
  - 25mg, 50mg, 100mg suppositories
  - 75mg/3mL injection
*By rectum*, 100mg at night, or, every 18 hours if higher dose required. Max. dose by any route is 150mg in 24 hours
In *June 2013 Drug Safety Update*, the MHRA issued new contraindications and warnings for diclofenac following a review of the cardiovascular risk, which it states is similar to that of the selective COX-2 inhibitors (see below).

**COX-2 selective inhibitors**
Not recommended for routine prescribing, however, may be required for patients with ankylosing spondylitis, and selected patients with rheumatoid arthritis.

- **Etoricoxib**
  - 60mg, 90mg tablets
In *October 2016 Drug Safety Update*, the MHRA updated their guidance for dose of etoricoxib for ankylosing spondylitis and rheumatoid arthritis. The lowest effective daily dose should be used, and the need for treatment should be regularly reassessed.
10.1.3 DRUGS THAT SUPPRESS THE RHEUMATIC DISEASE PROCESS

Initiation of rheumatoid disease modifying drugs is under the direct care of the Consultant Rheumatologist and prescribing may be transferred from primary care via a shared care agreement. These drugs are, in general, potentially toxic to the liver, kidneys and bone marrow, and the individual agents may have other potentially serious adverse effects. Patients should be intensively monitored after initiation of therapy or increases in dose, until a maintenance dose is reached, at which time less frequent monitoring may be acceptable.

These drugs include:
- Azathioprine
- Ciclosporin
- Hydroxychloroquine
- Leflunomide
- Methotrexate
- Mycophenolate mofetil
- Sulfasalazine

Rarely, intramuscular gold or penicillamine may be prescribed.

**NPSA Alert No. 13:** The use of methotrexate is the subject of a National Patient Safety Agency (NPSA) alert. The NPSA advice is:

- When prescribing weekly methotrexate the days of the week on which methotrexate should not be taken must be scored out and for discharge prescriptions the form, strength, dose and directions must be written in full.
- Patients must be counselled about the frequency of dosing, i.e. that it is a weekly dose and should understand their dose in milligrams as well as the number of tablets they should take.
- Before initiation of methotrexate therapy, patients must have undergone baseline assessment and tests.
- Patients must be counselled about the importance of having regular blood monitoring for toxicity and provided with written information and should consent to treatment.
- Only 2.5mg methotrexate tablets will be stocked at COCH, 10mg tablets will not be issued to patients as this has been associated with fatalities elsewhere due to errors in dosing.
- Patients taking methotrexate who present with breathlessness, dry persistent cough, vomiting or diarrhoea should be reviewed as a matter of urgency.
- Adherence to the Trust Medicines Policy in the prescribing, dispensing and administration of methotrexate is vitally important.
Cytokine Modulators

The following cytokine modulators have been approved for use at COCH in line with the local treatment pathway and appropriate NICE guidance.

- **Abatacept** as per NICE TA195 and TA375 for RA and TA373 for polyarticular JIA
- **Adalimumab** as per NICE TA195 and TA375 for RA and TA373 for polyarticular JIA
- **Certolizumab** as per NICE TA375 for RA and TA383 for AS and NRAxSpA
- **Etanercept** as per NICE TA195 and TA375 for RA and TA373 for polyarticular JIA
- **Golimumab** as per NICE TA375 and TA225 for RA
- **Infliximab** as per NICE TA195 and TA375 for RA
- **Rituximab** as per NICE TA195 for RA
- **Tocilizumab** as per NICE TA247 and TA375 for RA
- **Secukinumab** as per NICE TA407 for AS (awaiting local guideline) & TA445 for PsA
- **Ustekinumab** as per NICE TA340 for PsA

Phosphodiesterase type-4 inhibitors

- **Apremilast** as per NICE TA433
10.1.4 DRUGS FOR THE TREATMENT OF GOUT

See local gout pathway

Acute attacks of gout

- **Naproxen**
  See preparations in section 10.1.1

- **Etoricoxib**
  120mg tablets (max 8 days)
  (see advice on COX-2 inhibitors in section 10.1.1)

- **Colchicine**
  500microgram tablets

GUIDELINES FOR THE MANAGEMENT OF ACUTE GOUT

- Consider standard NSAID as above (particularly NAPROXEN 750mg initially, then 250mg every 8 hours until attack has passed), unless they are contraindicated or patient has heart failure; ETORICOXIB 120mg once daily for up to 8 days is also an option.

- Consider COLCICHINE in patients in whom NSAIDs are contraindicated. In order to diminish the risks of adverse effects (especially diarrhoea) it should be used at a dose of 500micrograms BD until symptoms are relieved (usually between 5 and 14 days). Higher doses may occasionally be used on consultant rheumatologist advice only (maximum four times daily, but this carries a significantly higher side effect profile with little difference in efficacy). If the patient is elderly or has renal impairment:
  - Consider reducing dose to 500micrograms once daily (eGFR is 10-50 ml/min)
  - Avoid if eGFR less than 10ml/min unless under specialist supervision

  Colchicine should be avoided in those taking a cytochrome p450 inhibitor such as clarithromycin, erythromycin, ciclosporin, ketoconazole, ritonavir, verapamil and diltiazem. Those using a statin should stop this temporarily whilst on colchicine. Discontinue if diarrhoea develops (consider 500 micrograms once daily if GI disturbance is mild).

- Consider PREDNISOLONE 20-40mg daily for up to 7 days for patients in whom NSAIDs are contraindicated and who cannot tolerate colchicine.

- ALLOPURINOL should not be started during an acute attack since it can prolong an attack. It should be started two to three weeks after the pain has subsided.
Long term control of gout

First line

- **Allopurinol** 100mg, 300mg tablets

Second line

- **Febuxostat** 80mg, 120mg tablets
  
  To be used for patients intolerant of allopurinol or in whom allopurinol in contraindicated, according to NICE Guidance TA164

GUIDELINES FOR THE MANAGEMENT OF CHRONIC GOUT

- Consider prophylactic gout treatment if patient has a continued episode of gout, or if the patient has tophaceous gout, evidence of renal or joint damage or a serum urate greater than 0.6 mmol/L.

- There is a risk of precipitating an acute attack in the early stages of uric acid lowering treatment. ALLOPURINOL should be initiated at a low dose (e.g., 100mg daily) and titrated up by 100mg every month to reach and maintain a serum uric acid (SUA) level below 0.3mmol/L (max. 900mg daily in divided doses).

- For patients with cardiac or renal impairment, start with 50mg daily and titrate up by 50mg every month to a maximum of 200-300mg daily in mild to moderate renal impairment, 100mg daily if severe. In patients with cardiac disease, try to minimise the use of diuretics. However, if diuretic therapy is required, then bumetanide should be considered first line.

- If allopurinol is not tolerated or contraindicated, FEBUXOSTAT 80mg daily can be used. This can be titrated up to 120mg daily after 1 month to achieve the target SUA. Prophylaxis is required as the risk of flares is higher than with allopurinol.

- Starting COLCHICINE 500micrograms BD for 3 to 6 months or a standard NSAID, as above, for at least 1 to 2 months when uric acid lowering treatment is initiated may also minimise the risk of precipitating an acute attack of gout.

- If an acute attack occurs during uric acid lowering treatment, do not alter the dose of allopurinol / febuxostat and do not stop therapy. Treat the acute attack as outlined above. If patients develop a rash while taking allopurinol following a desensitisation regime may be an option.

- COLCHICINE 500micrograms BD can also be used to manage chronic gout. See acute gout section for further prescribing information for colchicine.
10.2.2 SKELETAL MUSCLE RELAXANTS
Used for the relief of chronic muscle spasm or spasticity Associated with chronic disease. They are not indicated for spasm associated with minor injuries

- **Baclofen**
  - 10mg tablets
  - Liquid 5mg/mL

- **Diazepam**
  - 2mg/5mL syrup
  - 2mg tablets

NB: the higher strengths of diazepam tablets have a “street value”, therefore on the advice of the Chester Drug Service, primary care and out-patient prescribing should be restricted to the 2mg strength only

- **Diazepam**
  - 5mg, 10mg tablets
  (These strengths are for use for hospital use only)

Nocturnal leg cramps

- **Quinine sulphate**
  - 200mg, 300mg tablets
  - Always state the quinine salt when prescribing
  - 200mg quinine sulphate $\equiv$ 300mg quinine bisulphate

An MHRA drug safety update published in June 2010 gives the following advice:

- Quinine is not a routine treatment for nocturnal leg cramps, and should only be used when cramps regularly disrupt sleep
- Before use of quinine for nocturnal leg cramps, the risks should be carefully considered relative to the potential benefits
- After a trial of at least 4 weeks, treatment should be stopped if there is no benefit. If treatment continues, the benefits should be assessed around every 3 months
- Patients should be warned not to exceed the recommended dose. Serious side effects including irreversible blindness and death may occur with overdose
- Thrombocytopenia is a rare but potentially life-threatening adverse reaction associated with quinine. Patients should be instructed to stop treatment and consult a physician if signs of thrombocytopenia occur, such as unexplained petechiae, bruising, or bleeding
- Quinine should not be prescribed or given to patients who have previously experienced any adverse reaction to quinine, including that found in beverages
10.3 DRUGS FOR THE USE OF SOFT TISSUE INFLAMMATION

10.3.2 RUBEFACIENTS AND OTHER TOPICAL ANTIRHEUMATICS

Rubefacients are not recommended for the treatment of osteoarthritis therefore none are listed in the formulary. They can be purchased over the counter for relief of muscle, tendon and joint pain. They act by counter-irritation.

Topical NSAIDs

Topical NSAIDs are recommended as a treatment option in the management of knee or hand osteoarthritis (NICE CG177). They should be applied with gentle massage on unbroken skin.

Hypersensitivity

Topical application of large amounts can result in systemic effects including hypersensitivity reactions such as rashes, angioedema and bronchospasm. Topical NSAIDs should therefore be used with caution in those with a history of NSAID induced asthma.

Preparations

There are a number of preparations available to prescribe as well as to buy over the counter. The preparation with the lowest acquisition costs should be prescribed.

- **Ibuprofen (Fenbid®)** 5% gel

CAPSAICIN

The 0.025% cream can be considered as an adjunct in the management of hand or knee osteoarthritis (see section 10.1.1.).

A 0.075% cream is licensed for the relief of pain in post-herpetic neuralgia (after lesions have healed), and may also be used in the management of other painful neuropathic conditions such as diabetic neuropathy.