10.1 DRUGS USED IN RHEUMATIC DISEASES AND GOUT

MANAGEMENT OF OSTEOARTHRITIS: NICE Guideline CG59

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 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 gastro-protective agent for those at particularly high risk of GI adverse effects e.g. age over 65 years, taking warfarin, or other co-morbidity. Care should be exercised when co-prescribing NSAIDs with low dose aspirin and /or corticosteroids, since this can increase the risk of gastrointestinal 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.

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/24hours

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.

Second line

**Naproxen at any dose is associated with a lower thrombotic risk than other NSAIDs**

- **Naproxen**
  - 250mg, 500mg tablets
  - 125mg/5mL suspension

By mouth, 250 - 500mg twice daily.

- **Diclofenac**
  - 25mg, 50mg e/c tablets
  - 75mg, 100mg m/r tablets
  - 50mg dispersible tablets
  - 25mg, 50mg, 100mg suppositories
75mg/3mL injection

*By mouth,* 25 - 50mg 3 times daily, after food. 75mg *SR tabs* one at night or one twice a day. 100mg SR tabs, one nocte. *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, 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). A summary of the guidance on the MHRA website is available [HERE](#).

- Mefenamic acid
  - 250mg capsules
  - 500mg tablets

*By mouth,* 250mg - 500mg TDS. For use in patients with dysmenorrhea

### COX-2 selective inhibitors

- Not recommended for routine prescribing – see below

  **NSAIDs and associated risks**
  
  COX-2 selective inhibitors are associated with an increased risk of thrombotic events (myocardial infarction and stroke) and should not be used in preference to non-selective NSAIDs unless specifically indicated (high risk of GI bleeding) and then only following a cardiovascular risk assessment.

- Patients treated with any COX-2 selective inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient.

- Non-selective NSAIDs may also be associated with a small increased risk of thrombotic events, particularly when used at high doses for long term. Maximum dose ibuprofen and diclofenac are associated with an increased risk. Naproxen is associated with a lower risk and low dose ibuprofen (below 1.2g/24hours) has not been associated with an increased risk of myocardial infarction.

- For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of COX-2 selective inhibitors, in particular cardiovascular, gastrointestinal and other risk factors.

- Review the continuing need for a NSAID

- Alternative treatments may include regular paracetamol, or standard NSAIDs.

- The option to prescribe GI protection should always be considered, particularly for ‘at risk’ patients including patients over the age of 65, those taking concomitant aspirin or warfarin or those with serious co-morbidity.

- Prescribers are reminded that for all NSAIDs (including COX-2 selective inhibitors), the lowest effective dose should be used, for the shortest duration necessary.

- For patients switched to chronic non-selective NSAIDs, consideration should be given to the possible need for gastro-protective treatments (e.g. lansoprazole 15-30mg once daily).

- For patients for whom it is no longer thought that a COX-2 / NSAID-type drug is needed, discontinue gastro-protection if previously prescribed.
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

- Methotrexate
- Hydroxychloroquine
- Sulfasalazine E/C
- Azathioprine
- Leflunomide

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

- **Abatacept** See
  - NICE guidance TA195 Rheumatoid Arthritis - drugs for treatment after failure of a TNF inhibitor
  - NICE guidance TA280 Abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

- **Adalimumab** See
  - NICE guidance TA130 Rheumatoid Arthritis - adalimumab, etanercept, infliximab
  - NICE guidance TA143 Ankylosing spondylitis
  - See NICE guidance TA195 Rheumatoid Arthritis - drugs for treatment after failure of a TNF inhibitor
  - See NICE guidance TA199 Psoriatic arthritis – treatment

- **Certolizumab** according to NICE TA186

- **Etanercept** See
  - NICE guidance TA130 Rheumatoid arthritis - adalimumab, etanercept, infliximab
  - NICE guidance TA143 Ankylosing spondylitis
  - NICE guidance TA195 Rheumatoid arthritis - drugs for treatment after failure of a TNF inhibitor
  - NICE guidance TA199 Psoriatic arthritis – treatment

- **Golimumab** according to
  - NICE TA220 (psoriatic arthritis)
  - NICE TA225 (rheumatoid arthritis, after the failure of previous anti-rheumatic drugs)
  - NICE TA233 (ankylosing spondylitis)

- **Infliximab** See
  - NICE guidance TA130 Rheumatoid Arthritis - adalimumab, etanercept, infliximab
  - NICE guidance TA195 Rheumatoid Arthritis - drugs for treatment after failure of a TNF inhibitor
  - NICE guidance TA199 Psoriatic arthritis – treatment

- **Rituximab** See NICE guidance TA195 Rheumatoid Arthritis - drugs for treatment after failure of a TNF inhibitor

- **Tocilizumab** according to
  - NICE TA247 (Rheumatoid Arthritis)
  - NICE TA238 (Arthritis, juvenile idiopathic, systemic)

For further guidance, refer to the Chester Biologics Pathway for Rheumatoid Arthritis
Chester biologic treatment pathway in rheumatoid arthritis

**1st line biologic**
- TNFi (IFX, ADA, ETN, CZP, GOM)
- RTX if TNFi CI
- TCZ/ETN if MTX intolerant

**2nd line biologic**
- Seropositive RA
- Seronegative RA
- Co-existent TNFi responsive disease (psoriasis/IBD etc.)
- Adverse event to TNFi (non-class effect) within 6mths
- IL6 driven disease*

**3rd line biologic**
- RTX
- 2nd TNFi (CZP)/ABT/TCZ
- 2nd TNFi (any)
- TCZ or if rel. or abs. CI
- 2nd TNFi (CZP)/ABT
- RTX

* e.g. Adult onset Still’s disease, JIA.

- TNFi = anti-TNF, ABT=abatercept, TCZ=tocilizumab, RTX=rituximab, IFX= infliximab, ADA= adalimumab, ETN= etanercept, CZP= certolizumab pegol, GOM= golimumab.
- If patient is in clinical remission (DAS28≤2.6 on 2 occasions 6months apart) consider decreasing frequency of TNFi leading potentially to eventual withdrawal.
10.1.4 DRUGS FOR THE TREATMENT OF GOUT

Acute attacks of gout

- **Naproxen or diclofenac**
  - See preparations in section 10.1.1
- **Etoricoxib**
  - 120mg tablets
  - (see advice on COX-2 inhibitors in section 10.1.1)
- **Colchicine**
  - 500microgram tablets

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 is contraindicated, according to NICE Guidance TA164

GUIDELINES FOR THE MANAGEMENT OF ACUTE GOUT

- Consider standard NSAIDs particularly, NAPROXEN 500mg BD or DICLOFENAC 50mg TDS as above, unless they are contraindicated or patient has heart failure; ETORICOXIB, 120mg once daily is also an option.
- Consider COLCICINE in patients in whom NSAIDs are contraindicated. In order to diminish the risks of adverse effects (especially diarrhoea) it should be used in doses of 500micrograms 2 -4 times daily until symptoms relieved, maximum of 6mg per course; do not repeat the course within 3 days. Higher doses may occasionally be used on consultant rheumatologist advice only. If the patient has renal impairment, a smaller dose may be effective.
- Consider PREDNISOLONE 40mg daily initially for 3 to 5 days gradually tapering to zero by 5mg reductions over 10 to 14 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.
GUIDELINES FOR THE MANAGEMENT OF CHRONIC GOUT

- Consider prophylactic gout treatment if patient has more than two attacks per year 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 allopurinol therapy. Allopurinol should be initiated at a low dose e.g. 100mg daily and titrated upward in response to uric acid levels over 1 to 3 weeks: usual maintenance dose 300mg od (max. 900mg daily); The aim of treatment is to reach and maintain a uric acid level below 0.36mmol/L.

  For patients with cardiac or renal impairment, start with 50mg daily 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.

- Starting colchicine 500micrograms BD or a standard NSAID, for example naproxen or diclofenac for at least one to two months when allopurinol treatment is initiated may also minimise the risk of allopurinol precipitating an acute attack of gout.

- If an acute attack occurs during allopurinol treatment, do not alter the dose of allopurinol 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.
GOUT MANAGEMENT PATHWAY
(Adapted from British Rheumatology Guidelines, Jordan et al)

EXCLUDE SEPTIC ARTHRITIS AND SUPPRESS PAIN AND INFLAMMATION

TREAT AS SOON AS POSSIBLE

1st NSAID (Naproxen or diclofenac or etoricoxib) (see 10.1.1) ± PPI
2nd Colchicine
3rd Corticosteroid (i.a, oral, im, iv)

Review at 4-6 weeks
Assess lifestyle factors, blood pressure and perform serum, urate, renal function & glucose in all patients

Further attacks (or risk factors +++)
Treat acute attack, when resolved add
Allopurinol* + prophylactic cover with low dose NSAID ± PPI or colchicine
(Risk of precipitating acute attacks for approx 12 months)
*Titrate allopurinol dose according to serum uric acid – aim for level below 0.36mmol/L. Dose can be titrated up to a maximum of 900mg/day.
Febuxostat may be used for patients intolerant to allopurinol or in whom allopurinol is contraindicated (NICE TA164)

DO NOT STOP ALLOPURINOL / FEBUXOSTAT DURING ACUTE ATTACKS

Resolution

All patients
• Optimise weight
• Increase exercise
• Modify diet
• Reduce alcohol
• Maintain fluid intake
• Treat underlying cardiovascular risk factors

Continuing acute attacks

Refer to specialist care
10.2 DRUGS USED IN NEUROMUSCULAR DISORDERS

10.2.1 DRUGS WHICH ENHANCE NEUROMUSCULAR TRANSMISSION

- **Edrophonium chloride** 10mg/mL injection
- **Pyridostigmine bromide** 60mg tablets

**Edrophonium test for the diagnosis of myasthenia gravis**

**Indications:** For the diagnosis of myasthenia gravis.

**Preparation:** Edrophonium chloride 10mg/mL ampoules

Edrophonium injection was previously marketed as Tensilon® hence the description ’Tensilon test’.

**Administration:** Adults - Test for myasthenia gravis:

A 1 mL syringe is filled with the contents of 1 ampoule (10mg) and 2mg (0.2mL) is given IV, the needle and syringe being left *in situ*.

If no adverse reaction occurs within 30 seconds, the remaining 8mg (0.8mL) is injected IV.

In adults with unsuitable veins, 10mg can be given by IM injection.

**Contra-indications:** Do not give to patients with mechanical intestinal or urinary obstruction.

Do not give to patients with known hypersensitivity to the drug.

**Warnings / Precautions:** As edrophonium may provoke a cholinergic crisis it is recommended that facilities for resuscitation should be available before use.

A syringe containing 1mg of atropine should be kept at hand to counteract severe cholinergic reactions.

**Interactions:** Depolarising muscle relaxants such as suxamethonium should not be used in conjunction with doses of greater than 10mg edrophonium, since neuromuscular blockade may be potentiated and prolonged apnoea may result.

**Symptoms of overdosage:** Bradycardia, arrhythmias, hypotension and bronchiolar spasm.

Perspiration, gastro-intestinal hypermotility and visual
disturbances may also occur.

**Treatment of overdose:**
- Atropine sulphate 1 to 2mg IV is an antidote to the muscarinic effects.
- Artificial ventilation should be instituted if respiration is severely depressed.

### 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 in-hospital use only)

**Nocturnal leg cramps**

- **Quinine sulphate**
  - 200mg, 300mg tablets
  - Always state the quinine salt when prescribing
  - 200mg quinine sulphate ≡ 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 CG59](#)).

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; these would usually be the following non-proprietary preparations:

- **Ibuprofen** 5% gel
- **Ketoprofen** 2.5% gel for up to 7 days only
- **Piroxicam** 0.5% 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.