10 Musculoskeletal and joint diseases

Also see
SIGN 123 - Early management of rheumatoid arthritis (Feb. 2011)
www.sign.ac.uk/pdf/QRG123.pdf
SIGN 121 - Diagnosis and management of psoriasis and psoriatic arthritis in adults (October 2010)
www.sign.ac.uk/pdf/qrq121.pdf
NICE MTA 195 - Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (August 2010)
http://www.nice.org.uk/guidance/ta195
NICE Clinical Guidance 88 - Low back pain http://www.nice.org.uk/guidance/cg88

10.1 - Drugs used in rheumatic diseases and gout
10.1.1 Non steroidal anti-inflammatory drugs (NSAIDs)

General Prescribing Points

- If pain is the only symptom without signs of inflammation then consider non-drug treatments (TENS, acupuncture, physiotherapy) or an appropriate analgesic. See section 4.7 for further information on the WHO analgesic ladder.
- For non-inflammatory conditions simple analgesics e.g. paracetamol or the opioid analgesics should be considered instead of NSAIDs.
- At regular full dosage NSAIDs are useful in the treatment of pain associated with inflammation. NSAIDs are more appropriate than paracetamol or the opioid analgesics in inflammatory conditions e.g. rheumatoid arthritis and in some cases of advanced osteoarthritis. NSAIDs can also be of benefit in back pain and soft-tissue disorders but should only be for short term use (<1 month).
- All NSAIDs should be prescribed at the lowest effective dose for the shortest possible duration.
- NSAIDs should be used with caution in the elderly (risk of serious side-effects and fatalities).
- During long term use of NSAIDs ensure appropriate monitoring and regular re-evaluation of clinical need.

Gastrointestinal (GI) / Cardiovascular (CV) Risk

- All NSAIDs, including COX-2 selective agents, are associated with cardiovascular and gastrointestinal adverse events. Consider discontinuing NSAIDs (standard and COX-2 selective) in patients who are at high risk of CV or GI adverse events unless the benefits outweigh the risks.
- In patients with previous GI ulceration, only use NSAIDs when there is no appropriate alternative.
- Current evidence suggests that the combination of NSAID (standard or COX-2 selective) and low dose aspirin may increase the risk of gastrointestinal side-effects.
- Gastroprotection with a formulary PPI (omeprazole or lansoprazole) should be used in high risk patients prescribed standard NSAIDs and Cox-2 selective agents:
  - Over 65 years
  - Past history of peptic ulceration, bleeding or perforation
  - Co-prescription of other medicines associated with GI problems e.g. steroids, SSRIs, warfarin
  - Long term NSAIDs
  - Serious co-morbidities e.g. CV or renal disease
- All NSAIDs, including COX-2 selective agents, are associated with impairment of renal function. In

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patients with an eGFR <30mmol/l NSAIDs should not be prescribed. If eGFR >30mmol/l monitor renal function and withdraw NSAID if renal function declines.

Choice of NSAID

Standard NSAIDs

1st Choice
- Naproxen (standard tablets)

2nd Choice
- Ibuprofen (standard tablets)

NSAID for perioperative pain following hip or knee arthroplasty

1st Choice
- Celecoxib

Prescribing Points

- There is little difference in anti-inflammatory activity between different NSAIDs at maximum doses; there is variation in individual patient response and tolerance.
- About 60% of patients will respond to any NSAID with an analgesic response usually apparent within a week and an anti-inflammatory response within three weeks. If appropriate responses, at maximum tolerated doses of the NSAID, are not obtained within these times, another NSAID should be tried.
- Ibuprofen is commonly used at doses of 1.2g daily or less to minimise side-effects. At this dose ibuprofen has little anti-inflammatory effect. Consider using standard analgesia i.e. paracetamol instead.
- A full anti-inflammatory effect for ibuprofen is achieved with maximum doses i.e. 2.4g daily.
- Naproxen (1g daily) is associated with a lower thrombotic risk. Ibuprofen (2.4 g daily) and diclofenac (150mg daily) are associated with an increased risk of thrombotic events.
- Modified release preparations should not be prescribed as initial treatment but may be of benefit in patients with inflammatory arthritis who remain symptomatic on standard preparations e.g. the treatment of night-time pain or early morning stiffness.
- In osteoarthritis, there is only a minor inflammatory component, and paracetamol (4g daily) has been shown to be effective in many patients. NSAIDs should only be used when there is an inflammatory flare up. Consider using a formulary choice topical NSAID rather than oral NSAIDs if only one or two joints affected.

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Use of non-formulary NSAIDs / Cox-2 selective agents

- Where at least 2 formulary choices of NSAIDs have been ineffective or not tolerated it is appropriate to consider alternative options taking into account individual drug risk/benefit profiles.
- COX-2 selective agents are NOT more effective than standard NSAIDs.
- Etoricoxib is associated with a higher risk of hypertension than standard NSAIDs therefore blood pressure should be checked before initiation of treatment, 2 weeks after initiation and periodically during treatment.
- Celecoxib is the NSAID of choice for perioperative pain following hip or knee arthroplasty. The full supply will be supplied to the patient on discharge. Switch to formulary NSAID (Naproxen or Ibuprofen) if ongoing analgesia is required.

10.1.2 Corticosteroids
10.1.2.1 Systemic corticosteroids

Systemic corticosteroids may be used by specialists in the management of some rheumatic diseases. See section 6.3.2 for further information about parenteral and oral steroids.

10.1.2.2 Local corticosteroid injections
Superficial Injections
1st Choice Hydrocortisone acetate

Prescribing Points
- Hydrocortisone is the preferred agent for injections for structures lying superficially.

Intra-articular injection
1st Choice Methylprednisolone
2nd Choice Triamcinolone acetonide
S - Triamcinolone hexacetonide

Prescribing Points
- In inflammatory conditions of the joints, particularly rheumatoid arthritis, an intra-articular injection of methylprednisolone or triamcinolone may be used to reduce pain and increase mobility.
- Intra-articular corticosteroid injections can cause flushing and may affect the hyaline cartilage. Each joint should usually be treated no more than 3 - 4 times in one year. Intra-articular injections should only be administered by appropriately trained staff.

10.1.3 Drugs which suppress the rheumatic disease process
Management of inflammatory arthritis

General Prescribing Points
- All disease modifying drugs (DMARDs) used in inflammatory arthritis have shared care protocols agreed with GPs. Guidance on blood monitoring and patient information leaflets for each drug and for drug combinations are available on the ADTC website accessible either via the NHS Fife intranet or at www.fifeadtc.scot.nhs.uk.
- All suspected cases of inflammatory arthritis should be referred urgently to the Rheumatology service within 4 weeks of symptom onset.

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Early aggressive treatment with a combination of disease modifying agents can prevent progression of the disease.

Patients who do not respond to at least 2 DMARDs at therapeutic doses, one of which should be methotrexate, within 6 months will be considered for biologic therapy.

**Drugs affecting immune response**

| S - Methotrexate tablets\(^\text{®}\) (only the 2.5mg tablet strength should be prescribed)  
Methotrexate prefilled pen (Metoject\(^\text{®}\)) |
| S - Azathioprine |
| S - Hydroxychloroquine |
| S - Leflunomide |
| S - Sulfasalazine (E.C. tablets only) |
| S - Ciclosporin (Capimune\(^\text{®}\))  
Ciclosporin 10mg Capsules and Liquid formulation (Neoral\(^\text{®}\)) |
| S - Mycophenolate Mofetil |
| S - Tacrolimus (prescribe by brand name only - Prograf\(^\text{®}\), Advagraf\(^\text{®}\)) |
| S - Apremilast (Otezla\(^\text{®}\)) |

**Prescribing Points**

- Disease-modifying anti-rheumatic drugs (DMARDs) can affect the progression of disease but may require 2–6 months of treatment for a full therapeutic response.
- Apremilast is approved for specialist initiation/recommendation only. For use in adult patients with psoriatic arthritis who have had an inadequate response with at least 2 prior DMARD therapies or who are intolerant of such therapies. (For use of apremilast in plaque psoriasis see section 13.5.2.).
- Ciclosporin preparations should be prescribed by brand name only due to differences in bio-availability.
- The formulary choice for ciclosporin is Capimune\(^\text{®}\) (10mg capsules and liquid formulation must be prescribed as Neoral\(^\text{®}\)).
- Patients on ciclosporin should be regularly monitored for adverse effects including hypertension and renal impairment.
- The use of oral methotrexate for non-malignant conditions such as rheumatoid arthritis has been highlighted nationally as a potential risk for fatal medication errors. See Appendix 10B for guidance on the safe use of methotrexate [appendix-10b-oral-methotrexate-in-non-malignant-conditions](#).
- Only the enteric coated versions of sulfasalazine are licensed for the treatment of rheumatoid arthritis.

**Cytokine modulators**

1st Choice  
**H - Baricitinib (Olumiant\(^\text{®}\))**  
**H - Belimumab (Benlysta\(^\text{®}\))**

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Prescribing Points

- Cytokine modulators should only be used in the treatment of rheumatoid arthritis and psoriatic arthritis after failure of at least 2 standard DMARDs, one of which must be methotrexate. In ankylosing spondylitis cytokine modulators should only be used after failure of at least 2 NSAIDs.

- Abatacept is approved for restricted use only in combination with methotrexate for use in patients with active rheumatoid arthritis as a 3rd line option after failure with at least 2 of the following agents anti-TNF, tocilizumab or rituximab.

- Golimumab is approved for restricted use only where the use of a once monthly injection would be clinically advantageous to the patient/service provider.

- Inflectra® is a biosimilar formulation of infliximab. It is recommended in all new patients. To avoid confusion infliximab should be prescribed by generic and brand name.

- Ustekinumab is approved for restricted hospital use only. For the treatment of psoriatic arthritis after failure with anti-TNFs (For use in plaque psoriasis refer to section 13.5.3.).

- Belimumab is approved for restricted use only as an add on therapy in adult patients with active, antiantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy.

- Baricitinib is approved for restricted use in patients with severe rheumatoid arthritis (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs. In patients with severe disease inadequately controlled by a TNF antagonist, it may be used in patients ineligible to use rituximab.

- Tocilizumab is recommended for the treatment of Giant Cell Arteritis (GCA) in adult patients. It is however subject to a 12 month clinical stopping rule. Treatment beyond 52 weeks should be guided by disease activity, physician discretion and patient choice

10.1.4 Gout and cytotoxic-induced hyperuricaemia

Also see Appendix 10C - Gout management Guidelines
Prescribing Points

Acute Attack

- Lifestyle advice should be given to patients presenting with gout. In particular obesity, dietary purine intake, and the amount and type of alcohol consumed should be discussed.
- NSAIDs and/or oral colchicine are first line agents for systemic treatment of acute gout.
- Acute attacks of gout need to be treated with maximum doses of NSAIDs.
- Colchicine is an alternative in patients in whom NSAIDs are contra-indicated. Colchicine should be used at a dose of 500mcg twice daily in acute gout. Dose adjustment is necessary in patients with renal impairment (See Appendix 10C).
- Opioid analgesics may be used in addition to or instead of NSAIDs or colchicine.
- Either intra-articular or oral corticosteroids can be used as second line therapy for the treatment of acute gout providing infection has been ruled out. Corticosteroids are used when NSAIDs or colchicine are contraindicated or toxicity has occurred. Corticosteroids must be used with caution in patients with cardiac impairment, diabetes mellitus or peptic ulcer disease.

Long-term Control

- Drugs for long-term control are usually started 1-2 weeks after the attack has settled.
- Allopurinol and febuxostat are not effective in treating an acute attack and may prolong it indefinitely if started during the acute episode.
- Allopurinol should be recommended to patients with recurrent acute attacks, gouty tophi, arthropathy or radiographic changes. It should be started at a low dose (100 mg daily). Urate levels should be checked every 4 weeks and the dose of allopurinol increased by 100mg every four weeks until a target urate level of <0.3mmol/l is reached or patient is on the maximum licensed dose of 900mg allopurinol daily. Doses above 300mg should be given in divided doses. Dose adjustment is necessary in patients with renal impairment (See Appendix 10C).
- Febuxostat should only be prescribed in patients where allopurinol is not tolerated, contra-indicated or ineffective at the maximum tolerated dose.
- Febuxostat is contra-indicated in patients with ischaemic heart disease and in heart failure patients.
- The initiation of long term treatment may precipitate an acute attack of gout, therefore an anti-inflammatory analgesic or colchicine should be used as a prophylactic. Standard NSAIDs should be continued for at least one month after the hyperuricaemia has been corrected. Colchicine at a dose of 500mcg twice daily should be continued for up to 12 months in those with normal renal function. In patients with renal impairment the colchicine dose should be adjusted and continued for 6 months (See Appendix 10C for dosing).
- Crystallisation of urate in the urine can occur with the uricosuric drugs and it is important to ensure an adequate urine output especially in the first few weeks of treatment.

10.1.5 Other drugs for rheumatic disease

Also see NICE Clinical Guidance 59 - Osteoarthritis [http://www.nice.org.uk/guidance/cg59]

Glucosamine


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Prescribing Points

➤ None of the licensed glucosamine products has been approved for use within Scotland by the Scottish Medicines Consortium (SMC).

➤ Glucosamine products should **not be prescribed** on the NHS. Glucosamine sulphate at a daily dose of 1500mg can be bought as an oral nutritional supplement. Patients should be advised to stop treatment if there is no symptomatic benefit after 3 months.

10.2 - Drugs used for Neuromuscular disorders

10.2.1 Drugs which enhance Neuromuscular transmission

1st Choice  
S - Pyridostigmine (Mestinon®)

2nd Choice  
S - Neostigmine

Prescribing Points

➤ Anticholinesterases are used in the treatment of myasthenia gravis.

10.2.2 Skeletal muscle relaxants

| Short term | 1st Choice | Diazepam |
| Long term | 1st Choice | Baclofen |
|           | 2nd Choice | S - Dantrolene  
|           |           | S - Tizanidine |
|           |           | H - Dantrolene IV |

Prescribing Points

➤ Baclofen is used to relieve chronic severe spasticity resulting from multiple sclerosis or spinal cord trauma. The dose should be increased slowly to avoid the major side-effects of sedation and muscular hypotonia. Slow withdrawal of baclofen over one to two weeks is recommended.

➤ Baclofen injection is restricted to use in specialist units only.

➤ Diazepam may be used to relieve muscle spasm of varied aetiology but should not be used for more than 5 days.

➤ Oral dantrolene may be used for chronic severe spasticity of voluntary muscle. It produces fewer central adverse effects making it a drug of choice. The dose should be increased slowly.

➤ Dantrolene IV is recommended for malignant hyperthermia.

➤ Tizanidine is an alpha2-adrenoceptor agonist indicated for spasticity associated with multiple sclerosis or spinal cord injury.

➤ Sativex® is a cannabinoid derivative licensed as an adjunct treatment for moderate to severe spasticity associated with multiple sclerosis in patients who have not responded adequately to other skeletal muscle relaxants. Sativex® has not been approved by the Scottish Medicines Consortium (SMC). **Sativex® should not be prescribed unless an Individual Patient Treatment Request has been approved by NHS Fife.** The dose should be titrated over 2 weeks; response to treatment should be reviewed after 4 weeks and treatment stopped if an adequate response is not achieved.

Nocturnal Leg cramps

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December 16  
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Quinine

Prescribing Points

➢ Quinine is not recommended for routine treatment of leg cramps due to its potential toxicity. Quinine should only be used when non-pharmacological treatments have not worked (e.g. passive stretching exercises); the cramps are very painful or frequent and cause regular disruption to sleep. Other treatable causes of cramp should be excluded.

➢ Quinine sulphate 200-300mg at bedtime can be trialled for 4 weeks. If there is no benefit after 4 weeks then treatment should be stopped.

➢ In long-term use, patients should be monitored for adverse effects and treatment should be interrupted at intervals of 3 months to assess the ongoing need for treatment.

➢ Quinine is very toxic in overdose and immediate emergency treatment is essential.

10.3 - Drugs in relief of soft-tissue inflammation and topical pain relief

10.3.1 Enzymes

**H - Hyaluronidase (Hyalase®)**

**H - Collagene clostridium histolyticum (Xiapex®)**

Prescribing Points

➢ Collagenase clostridium histolyticum is approved for the treatment of Dupuytren’s contracture in adult patients with a palpable cord as an alternative to limited fasciectomy in patients with moderately severe Dupuytren’s contracture.

➢ Collagenase clostridium histolyticum is not recommended for use by the SMC for the treatment of Peyronie’s disease. Requires submission and approval of an SMC Non Submission Treatment Request Form before prescribing for this indication.

10.3.2 Rubefacients, topical NSAIDs, capsaicin

Also see NICE Clinical Guidance 59 - Osteoarthritis [http://www.nice.org.uk/guidance/cg59](http://www.nice.org.uk/guidance/cg59)

**Topical NSAIDs**

1st Choice

Ibuprofen gel

2nd Choice

Diclofenac diethylammonium 1.16% gel (Voltarol Emulgel®)

Prescribing Points

➢ Topical NSAIDs may be used for short term acute treatment of sprains and strains (up to 7 days).

➢ NICE Clinical Guidance 59 (Osteoarthritis) recommends the use of topical NSAIDs ahead of oral NSAIDs in osteoarthritis affecting an individual joint.

➢ Topical NSAIDs in the treatment of osteoarthritis should only be considered for treatment of the hands and knees. If treatment has been ineffective after 4 weeks then it should be discontinued.

➢ Oral NSAIDs should not be prescribed concomitantly with topical NSAIDs.

➢ Patients should be advised against excessive exposure to sunlight of areas treated with topical NSAIDs in order to avoid the possibility of photosensitivity.

➢ Care should be taken when prescribing diclofenac gel. Only the 1.16% strength (Voltarol Emulgel®) is...
The evidence available does not support the use of topical rubefacients in acute or chronic musculoskeletal pain.

**Capsaicin**

- **Capsaicin 0.025% cream (Zacin®)**
- **S - Capsaicin 0.075% cream (Axsain®)**

**Prescribing Points**

- Capsaicin is a counter-irritant which may cause a transient burning sensation when applied. It should be applied four times daily in all patients. Less burning is reported at this frequency of application.
- Capsaicin works by depleting Substance P in nerve ends. The process can take about 4 weeks. Benefits to patients and need for continuing treatment should be assessed after 6-8 weeks.
- Capsaicin 0.025% (Zacin®) is indicated for use in hand or knee osteoarthritis. It may also be initiated for neuropathic pain before stepping up to the 0.075% strength.
- Capsaicin 0.075% (Axsain®) is restricted for use in patients with diabetic neuropathy on the advice of diabetologists or neurologists and for refractory cases of post-herpetic neuralgia (ONLY after lesions have healed). Capsaicin 0.075% may also be initiated by consultants in chronic pain management for various other neuropathic problems.

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December 16

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