Pharmacological treatments can have a major impact on the outcome of rheumatic diseases. To achieve the best results, individual treatment regimens comprising analgesic agents, non-steroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs are used. The success of the latter two groups of drugs in controlling symptoms and suppressing disease processes is tempered by their potential for adverse effects.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the drugs most commonly prescribed by general practitioners, reflecting the high prevalence of rheumatic diseases in the community — up to 10% of people have a rheumatic symptom at any one time.

The NSAIDs currently available come from a variety of chemical classes but have a common mechanism of action — interference with the synthesis of prostaglandins, which are important mediators of pain and inflammation. As prostaglandins also play a key role in maintaining normal gastric and renal function, any interference with these processes may produce adverse effects in these systems.

Recently, it has been shown that the cyclooxygenase enzyme system involved in producing prostaglandins is composed of two enzymes: a constitutive enzyme (Cox 1) produces prostaglandins for normal bodily functions (e.g., gastroprotection and renal perfusion), and an inducible enzyme (Cox 2) produces prostaglandins found at sites of tissue inflammation. Some of the newer NSAIDs, such as nabumetone, seem to have a selective effect on Cox 2 rather than on Cox 1, and may therefore be associated with lower incidences of gastric and renal side effects. A new class of NSAIDs now undergoing clinical trials are highly selective for Cox 2, but their advantages, in particular for the gastrointestinal tract, remain to be determined.

NSAIDs are used widely in the treatment of inflammatory forms of arthritis, such as rheumatoid arthritis or the seronegative arthropathies; they form the mainstay of symptomatic treatment, although they do not affect the disease process. However, in osteoarthritis, NSAIDs should not be used as a first-line drug, but only for patients not responding to other analgesics, and only for short periods. The lowest possible dose required to control symptoms should be employed and the least-toxic NSAID, such as ibuprofen, should be tried first.

The major adverse effects of NSAIDs are shown in Box 1. Adverse effects are relatively common, but with care in prescribing they can be reduced to a minimum. For the gastrointestinal tract and the kidney, the common adverse effects are dose related. Just as there is variability in response to NSAIDs in terms of efficacy, there is also variability in response in terms of adverse effects. The occurrence of an adverse reaction (e.g., dyspepsia) to one NSAID does not necessarily mean that the same adverse event will occur with another NSAID.
<table>
<thead>
<tr>
<th>Gastrointestinal (common)</th>
<th>Dermatological (rare)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigestion, ulceration, haemorrhage</td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td>Small-bowel ulceration</td>
<td>Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
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<tr>
<td>Stomatitis</td>
<td>Bullous eruptions</td>
</tr>
<tr>
<td><strong>Renal</strong> (common)</td>
<td>Benign morbilliform eruptions</td>
</tr>
<tr>
<td>Transient rise in serum creatinine level</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Renal failure</td>
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<tr>
<td>Oedema</td>
<td>Urticaria</td>
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<tr>
<td>Interstitial nephritis</td>
<td>Pustular psoriasis</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td><strong>Haematological</strong> (rare)</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Aplastic anaemia</td>
</tr>
<tr>
<td><strong>Neurological</strong> (uncommon)</td>
<td>Red-cell aplasia</td>
</tr>
<tr>
<td>Headache</td>
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<tr>
<td>Aseptic meningitis</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Nausea</td>
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<td><strong>Pulmonary</strong> (rare)</td>
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<td>Asthma</td>
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<tr>
<td>Pulmonary oedema</td>
<td>Anaphylactoid reactions</td>
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<tr>
<td>Pulmonary alveolitis</td>
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</tbody>
</table>

**Adverse effects**

**Gastrointestinal**
All NSAIDs have the potential to cause dyspepsia, although the occurrence of symptoms does not seem to predict any particular gastric condition. Symptoms are reported in up to 40% of patients taking NSAIDs, and include gastric erosion, peptic ulcer formation and perforation, major gastrointestinal haemorrhage, and inflammation and change in the permeability of the intestine. Two recent studies suggest that there may be a hierarchy of NSAIDs in their potential to cause gastric side effects, contrary to previous beliefs, with ibuprofen being the least gastrotoxic. Clear evidence also exists of factors which increase the risk of NSAID-associated gastrointestinal toxicity (Box 2).

**Renal**
Prostaglandins are involved in the regulation of renal blood flow and glomerular filtration. NSAIDs commonly cause reversible impairment of glomerular filtration and, rarely, acute renal failure, oedema, interstitial nephritis, papillary necrosis, chronic renal failure and hyperkalaemia. No NSAID can be prescribed with absolute safety for the kidney, but renal adverse events are more likely to occur in patients with decreased glomerular filtration (because of hypovolaemic states, such as hypoalbuminaemia or in the perioperative period), and in those with pre-existing renal impairment (because of age, atherosclerosis and underlying renal disease, such as that associated with hypertension).

NSAIDs can also cause a slight increase in blood pressure in many patients and interfere with the effect of several antihypertensive agents.

**Haematological**
Aplastic anaemia, thrombocytopenia, neutropenia and haemolytic anaemia are rare reactions to some NSAIDs. Iron deficiency as a consequence of blood loss from the gastrointestinal tract is the most common haematological adverse event, as all NSAIDs inhibit platelet function. Aspirin contrasts with other NSAIDs by inhibiting platelet function irreversibly. After aspirin is withdrawn platelet function takes four to five days to return to normal, but with other NSAIDs it takes about three half-lives. Thus, these drugs need to be discontinued for variable periods before inhibitory effects on platelets cease (an important consideration in some branches of surgery).

**Hepatic**
Salicylates are often associated with an increase in liver enzyme levels, but a transient increase may also occur with other NSAIDs. This has been most commonly reported with drugs such as diclofenac or sulindac, but resolves rapidly on drug withdrawal.

**Neurological**
Mild central nervous system side effects are often seen with NSAIDs but are sometimes not appreciated as such. Severe headache has been associated with indomethacin therapy, and some patients report drowsiness or subtle personality and thought-processing changes when taking NSAIDs. Although aseptic meningitis has been reported with ibuprofen and sulindac therapy, this is usually in patients who may develop this condition as part of their underlying disease, such as systemic lupus erythematosus, and it may not be a true drug-associated adverse event.

### 2: Risk factors for gastric toxicity of non-steroidal anti-inflammatory drugs (NSAIDs)

**Definite**
- Age over 65 years
- Prior ulcer disease or complication
- High dose, multiple NSAIDs
- Concomitant corticosteroid therapy
- Short duration of therapy (<3 months)

**Possible**
- Condition necessitating NSAID treatment (e.g., rheumatoid arthritis)
- Female sex
- Smoking
- Alcohol
- Presence of *Helicobacter pylori*

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Pulmonary

Several NSAIDs, including aspirin, may exacerbate bronchospasm in adult asthmatic patients, perhaps because of inhibition of pulmonary prostaglandin production. Care should be taken in prescribing NSAIDs to asthmatic patients and they should be asked if they have noted an increase in bronchospasm with other NSAIDs or aspirin.

Dermatological

Skin reactions such as erythema multiforme, bullous eruptions or photosensitivity have been reported. It seems that drugs with a long half-life are more commonly associated with skin reactions, but most reactions are relatively mild and settle rapidly when the drug is withdrawn.

Interactions of NSAIDs with other drugs

As NSAIDs are commonly used in older persons, the potential for drug interactions is high (Box 3). Care should always be taken when an NSAID is added to a complex therapeutic regimen and the patient should be observed for potential drug or drug–disease interactions.7

A case history of gastric adverse effects in a woman with rheumatoid arthritis is discussed in Box 4.

A 45-year-old woman with longstanding rheumatoid arthritis was admitted to hospital with acute haematemesis. She was taking 20 mg piroxicam, 5 mg prednisone and 10 mg methotrexate weekly. Endoscopy of the upper gastrointestinal tract revealed extensive gastric erosions.

Concomitant corticosteroid therapy, female sex and rheumatoid arthritis were other factors contributing to the overall risk of ulcer complications in this patient (Box 2).

No firm guidelines have been established for treatment of peptic ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs). There is evidence that ulcers heal reasonably well with H₂-receptor antagonists, even though NSAIDs are continued.5 Despite these findings, NSAIDs should be withdrawn whenever possible, to promote more rapid ulcer healing, especially with a potentially life-threatening complication, as in this patient.

To prevent a flare of arthritis, the dose of prednisone may be raised temporarily to 10 mg daily. Prophylactic therapy with vitamin D analogues (e.g., calcitriol or bisphosphonates) to reduce vertebral bone loss, should be considered if corticosteroids in doses exceeding physiological replacement are continued for any length of time.6 Ulcer healing can be expected within 6–12 weeks of therapy with full doses of an H₂-receptor antagonist or omeprazole, and reintroduction of an NSAID such as ibuprofen may be considered.
Disease-modifying antirheumatic drugs

Most patients with rheumatoid arthritis who develop joint erosions will do so within the first two years of the disease. Thus, the disease-modifying antirheumatic drugs (DMARDs), which reduce disease activity, should be introduced as soon as possible after the diagnosis has been confirmed. The commonly used DMARDs and their major adverse effects are shown in Box 5. Adverse effects and the development of “resistance” lead to most patients having to stop taking the drug within four years. 

Comparative studies show that DMARDs have similar rates of toxicity to NSAIDs. Meta-analysis of randomised controlled trials of DMARDs shows a favourable benefit-to-toxicity ratio for low dose methotrexate and antimalarial drugs compared with other DMARDs, such as gold salts, D-penicillamine, sulphasalazine and azathioprine. Hydroxychloroquine and auranofin, with similar toxicities, are significantly less effective than other DMARDs but still significantly better than placebo.

**Chloroquine and hydroxychloroquine**

The antimalarials (chloroquine and hydroxychloroquine) have been shown to be effective in patients with rheumatoid arthritis and systemic lupus erythematosus. Both drugs have a particularly long half-life, so it may take three to four months before steady state concentrations are reached and maximal efficacy is achieved. Adverse effects include indigestion, skin rash and visual disturbances, with retinopathy being the most serious. Severe retinal toxicity, however, is extremely rare with currently recommended doses (chloroquine diphosphate, < 5mg/kg per day; and hydroxychloroquine sulfate, 7.5 mg/kg per day). Periodic visual assessment is recommended twice a year, although a formal evaluation of this monitoring has not been performed.

**Sulphasalazine**

Sulphasalazine has been shown to slow joint erosions in rheumatoid arthritis, and, although up to 50% of patients may develop adverse effects, only half will be severe enough to stop treatment. Adverse effects include skin rashes, nausea and abdominal pain, hepatic enzyme abnormality, central nervous system disturbances and blood dyscrasias, particularly in patients with glucose-6-phosphate dehydrogenase deficiency. Gastric side effects are reduced by enteric coating, and most serious adverse effects seem to occur within the first four months of treatment. Other effects, such as discoloration of urine and sweat as well as oligospermia, need to be discussed with the patient, but they revert to normal when the treatment is withdrawn.

**Gold complexes**

Gold complexes, both oral and intramuscular, have a number of actions (Box 5), and have been used for a long time for treatment of rheumatoid arthritis. Intramuscular gold is still one of the most effective of the DMARDs. It can be used for long periods in doses of 10–50 mg at varying intervals (usually weekly initially and then four- to six-weekly), with up to 35% of patients having an excellent clinical response, peaking at 12 months. Long term remissions, however, are rare and side effects occur commonly. These include skin rashes, mouth ulcers, and, rarely, thrombocytopenia, neutropenia and bone-marrow aplasia, proteinuria, hepatitis, enterocolitis, and pulmonary manifestations, such as pneumonitis. Also, neuropathy, exfoliative dermatitis and chrysalis are rarely reported.

**D-Penicillamine**

D-Penicillamine is rarely used now in the management of rheumatoid arthritis. Its major adverse effects usually occur in the first six months of treatment and lead to drug with-
drawal in about a quarter of patients. Major reactions to penicillamine include skin rashes, proteinuria–haematuria (with or without glomerulonephritis), stomatitis, thrombocytopenia, neutropenia and a variety of autoimmune phenomena (e.g., a positive antinuclear factor, myasthenia gravis, polymyositis and Goodpasture's syndrome). Adverse reactions to D-penicillamine are more frequent in patients with a poor capacity for producing sulfoxides,20 and there is also an association between toxicity and the human leucocyte antigens HLA-DR3 and HLA-B8.

**Methotrexate**

Methotrexate, given in weekly pulse doses, has now become the most commonly prescribed DMARD. It is eliminated by renal excretion and care has to be taken in patients with renal insufficiency. Recent studies show that patients are able to continue taking methotrexate for longer than other DMARDs and that it works reasonably quickly (within one to two months).19 Long term hepatic toxicity with methotrexate is still a concern and guidelines have just been established by the American College of Rheumatology (ACR).21 The ACR guidelines suggest that pretreatment liver biopsy should be considered only in patients with a history of excessive alcohol consumption, persistently abnormal baseline liver enzyme levels or chronic hepatitis B or C infections. Liver enzymes and albumin levels should be monitored at four- to six-week intervals, and liver biopsy performed only in patients with persistently abnormal levels. These guidelines have recently been shown to be clinically useful in prospective tests in over 100 patients treated with methotrexate, although it is now recommended that insulin-dependent diabetes mellitus be added to the original ACR list of risk factors for methotrexate hepatotoxicity.22

**Azathioprine, cyclophosphamide and chlorambucil**

Azathioprine, cyclophosphamide and chlorambucil are still used in some patients with refractory disease. Care should be taken with these agents as they have significant immediate toxicity and are also associated with an increased incidence of neoplasia. Patients treated with azathioprine have an increased rate of lymphoproliferative disorders and other malignancies.23 Cyclophosphamide is associated with haemorrhagic cystitis and leads to substantial immunosuppression, with an increased risk of infection and suppression of gonadal function. Cyclophosphamide is also associated with a significant increase of neoplasia, particularly bladder and skin cancers, and this risk of malignancy may continue for many years after discontinuation of the drug.24

**Cyclosporin**

Cyclosporin has recently been advocated for the treatment of severe rheumatoid arthritis but its use is restricted because of its significant cost and its propensity to interfere with renal function and cause a rise in blood pressure, although these

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**Case history — mild proteinuria and microscopic haematuria in a man with rheumatoid arthritis**

Rheumatoid arthritis in a 53-year-old man had been reasonably well controlled for 12 months with monthly injections of 50 mg aurothioglucose, and 250 mg naproxen twice daily. Mild proteinuria (++) and microscopic haematuria were discovered. Quantitative proteinuria measurements (450 mg/day) and serum creatinine level and creatinine clearance remained within normal limits. The patient felt well and showed no clinical evidence of any other adverse effects related to gold compounds or naproxen.

Widespread renal effects occur with both non-steroidal anti-inflammatory drugs (NSAIDs) and with gold compounds.

Inhibition of prostaglandin synthesis by NSAIDs leads to a decrease in renal blood flow, excretion of water and sodium, and the production of renin. This occurs particularly in elderly, dehydrated patients with pre-existing impaired kidney function, and sometimes causes acute renal failure. The combination of an acute urine sediment and proteinuria due to interstitial nephritis has been described in patients taking naproxen, indomethacin, fenoprofen and tolmetin.20 Onset most often occurs from two weeks to 18 months after initiation of NSAID therapy. Renal failure may be sufficiently severe to require intermittent dialysis support. Resolution time varies from as little as one month to almost a year after drug withdrawal.

On the other hand, transient proteinuria and microscopic haematuria are frequent findings during treatment with injectable gold complexes. These symptoms have a good chance of resolving spontaneously after drug withdrawal, but they may also be a warning of a more severe glomerulo-

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Changes invariably return to normal once the drug is withdrawn.23

Combinations of DMARDs

Recent studies of treatments with two or more DMARDs are currently being undertaken. Combination treatment with methotrexate and sulfasalazine has been shown to be superior to methotrexate treatment alone,26 and the addition of cyclosporin to methotrexate alleviated rheumatoid-arthralgia-related symptoms significantly in patients with primary or secondary failure to respond to methotrexate.27 Recently, O’Dell et al.28 have demonstrated the benefits of a combination of weekly methotrexate, sulfasalazine and hydroxychloroquine over methotrexate and methotrexate plus sulfasalazine over a two-year period, without an increase in toxicity. Combinations of DMARDs are increasingly being prescribed; however, more studies are needed to confirm their value.

Corticosteroids

Corticosteroids are still commonly used in the management of rheumatic diseases and a recent study has demonstrated that in doses of 7.5 mg a day they slow the erosion rate in rheumatoid arthritis.29 Corticosteroids can be used in the treatment of inflammatory joint disease and in the following situations:

- As continuous oral background therapy (up to 7.5 mg daily).
- In short courses of a rapidly decreasing dose for disease flares.
- As large oral pulse doses (100 mg to 1 g).
- As intra-articular injections into inflamed joints.
- As intravenous pulses after a flare or as induction treatment at the time of commencement of DMARDs.

Corticosteroids are associated with a wide variety of side effects in the long term, including cushingoid appearance, diabetes, hypertension, osteoporosis, skin fragility, slowness of wound healing and increased susceptibility to infection.

A case history of adverse effects of drug therapy in a man with rheumatoid arthritis is discussed in Box 6.

Conclusion

Rheumatoid arthritis and other forms of inflammatory arthritis require aggressive and continuing therapy if joint erosion is to be slowed and long-term disability reduced. All antirheumatic drugs have, like most other medications, great potential for benefit as well as harm. Careful and continuous review of patients is essential to reduce the risk of serious toxicity from these drugs.

Acknowledgement

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References