

- irrespective of the dose, kind or frequency of NSAIDs taken, no significant difference was reported to exist overall between NSAID users who described any current drinking, those who were ex-drinkers, and those who never drank.

There is no proof that mild to moderate alcohol use significantly increases the risk of upper gastrointestinal bleeding in patients taking aspirin, especially if the aspirin is taken only as needed. However, people who consumed **at least** 3–5 drinks daily and who regularly took more than 325 mg of aspirin did have a high risk of bleeding.

Commercial considerations

The Medicines Evaluation Committee, while acknowledging the evidence, did not recommend an alcohol warning on labels of aspirin products. A similar warning which appears on US labels of paracetamol with 'liver damage' replacing 'stomach bleeding' was also rejected for Australia. The issue is whether, in order to maintain a degree of commercial parity in the highly competitive over-the-counter analgesic market, both paracetamol and aspirin/NSAIDs should have an alcohol statement (for different reasons) or neither should have it. Anything that will encourage product differentiation can operate to favour one product or, on the other hand, disadvantage its competitor by invidious comparison. Media advertisements that use the term 'gentle to the stomach' for paracetamol suggest, by innuendo, that other over-the-counter analgesics might be less than gentle. However, for most people, the use of over-the-counter doses of aspirin, ibuprofen or paracetamol carries little risk. The regulatory

authorities therefore decided not to interfere in the market by imposing mandatory warning labels.

What do clinicians do?

At-risk patients need to be identified. Patients may understate their consumption of alcohol and not think that aspirin and other over-the-counter NSAIDs can cause problems. The clinician may need to alert patients to the risks of all medicines, not just those obtained on prescription. Heavy drinkers who regularly take aspirin are at particular risk of gastrointestinal bleeding.

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Further reading

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Conflict of interest: none declared

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Articaine hydrochloride with adrenaline

Septanest, Deltazine, Bucanest (Specialites Septodont)

1.7 mL glass cartridges containing 4% articaine and 1 in 100 000 adrenaline

Approved indication: dental anaesthesia

Australian Medicines Handbook section 2.4

Articaine is a local anaesthetic that has been approved overseas for several years. Like other amide anaesthetics, articaine blocks nerve conduction when it is infiltrated around a nerve. This action is prolonged by combining the drug with a vasoconstrictor such as adrenaline.

The combination of articaine and adrenaline can be used for local or regional anaesthesia for dental procedures. Anaesthesia begins within six minutes and lasts for an hour. The half-life of

articaine is approximately 1.8 hours. It is metabolised and then mainly excreted in the urine.

Articaine 4% with adrenaline was compared with lignocaine 2% with adrenaline in three double-blind trials. The drugs were given as submucosal infiltrations or nerve blocks before dental procedures. There were no significant differences, on a visual analogue pain scale, between the anaesthesia achieved by the 882 patients given articaine and the 443 given lignocaine.¹

Approximately one patient in five reported an adverse event after dental anaesthesia. The most common complaint in both groups was postoperative pain, followed by headaches and facial swelling. Although the incidence was less than 1%, paraesthesia and hypoesthesia affected more of the patients treated with articaine. Although some patients developed changes in pulse and blood pressure these could have been related to anxiety

about the injection and the procedure.² As with other local anaesthetics it is important that the drug is not injected into a blood vessel. The dental surgery should have resuscitation equipment in case of cardiovascular collapse or convulsions. Although the immunogenic potential of articaine is probably low, it is contraindicated in patients with an allergy to sodium metabisulfite as the formulation includes this antioxidant.

Widespread use of articaine has allowed rare adverse effects to emerge. For example, there may be paralysis of the ocular muscles after posterior, superior alveolar injections of articaine.³ Although the efficacy of articaine appears to equal that of lignocaine, there does not seem to be a compelling clinical reason for Australian dentists to change their choice of local anaesthetic.

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Efalizumab

Raptiva (Serono)

vials containing 125 mg lyophilised powder for reconstitution

Approved indication: psoriasis

Australian Medicines Handbook section 8.6.1

The recognition of psoriasis as an autoimmune disorder has prompted research into the role of T-lymphocytes. The activation of these lymphocytes involves leukocyte-function associated antigen type 1 (LFA-1). By binding to LFA-1 efalizumab reduces inflammation by inhibiting the adhesion of T-lymphocytes to other cells.

Efalizumab is a monoclonal antibody produced by genetic engineering. Although it is produced using Chinese hamster ovary cells, the molecule is humanised. Efalizumab has to be given by weekly subcutaneous injections.

A placebo-controlled trial of efalizumab enrolled 556 patients with chronic plaque psoriasis covering at least 10% of their bodies. After 12 weeks 27% of the patients given efalizumab (1 mg/kg) had at least a 75% improvement in their psoriasis area and severity index (PASI). Only 4% of the patients given a placebo had a similar response.¹

Another placebo-controlled trial treated 597 patients weekly for 12 weeks then re-randomised patients who had responded to efalizumab to continue treatment for another 12 weeks, reduce to fortnightly injections, or switch to placebo. Patients whose

PASI had not improved were re-randomised to take a higher dose or a placebo for another 12 weeks. After the first 12 weeks there was a 75% improvement in the PASI in 5% of the patients given weekly injections of placebo. This outcome was achieved by 22% of the patients given efalizumab 1 mg/kg and 28% of those given 2 mg/kg. The improvement was sustained in most of the patients who responded and were re-randomised to continue treatment. The response was only maintained by 20% of the responders who were switched to a placebo. Only 13% of the patients who did not initially respond achieved a PASI improvement of 75% when treated with a higher dose.² Although a dose of at least 2 mg/kg was used in the patients who continued treatment after 12 weeks, the recommended weekly dose in Australia is 1 mg/kg with a maximum single dose of 200 mg.

As efalizumab affects the immune system there is a potential for serious adverse effects such as malignancy and lymphoproliferative disorders. Patients should have their blood counts checked as lymphocytosis and thrombocytopenia can occur. Flu-like symptoms such as headache, fever and chills are significantly more common with efalizumab than with placebo. As adverse reactions may be more frequent early in treatment an initial dose of 0.7 mg/kg is recommended. Efalizumab is potentially immunogenic. Approximately 8% of patients will have an allergic reaction and some will develop anti-efalizumab antibodies. Information about the long-term safety of efalizumab is limited, but there is a risk of the psoriasis getting worse if the drug is stopped abruptly.

In Europe efalizumab is restricted to patients who have failed to respond to treatments such as cyclosporin, methotrexate or phototherapy. This restriction does not apply in Australia, but there is a need to investigate if efalizumab is more effective than other systemic therapies for chronic plaque psoriasis.

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1. Efalizumab Study Group. Efalizumab for patients with moderate to severe plaque psoriasis. *JAMA* 2003;290:3073-80.
2. Efalizumab Study Group. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003;349:2004-13.

Fosamprenavir calcium

Telzir (GlaxoSmithKline)

700 mg tablets

225 mL bottles containing 50 mg/mL suspension

Approved indication: HIV infection

Australian Medicines Handbook section 5.4.3

Amprenavir is a protease inhibitor that can be used in combination with other drugs to treat patients infected with HIV.¹ It can be given with ritonavir as their interaction

significantly increases the plasma concentration of amprenavir (see New drugs, Aust Prescr 2002;25:44-7).

Fosamprenavir has been developed to try and overcome some of the pharmacological disadvantages of amprenavir, such as low solubility. It is a prodrug which is rapidly converted to amprenavir during absorption. Fosamprenavir can also be given with low dose ritonavir to increase the concentration of amprenavir.

Fosamprenavir was compared with nelfinavir in a study of patients who had not previously received antiretroviral drugs. Each group of patients also received abacavir and lamivudine. After 48 weeks 66% of the 166 patients given fosamprenavir and 51% of the 83 patients given nelfinavir had less than 400 copies of viral RNA/mL. The median increase in CD₄ cell counts was 201 cells/mm³ in the fosamprenavir group and 216 cells/mm³ in the nelfinavir group.²

Another study enrolled 315 patients who had previously been treated with protease inhibitors. This compared regimens of fosamprenavir and ritonavir to a regimen of lopinavir and ritonavir. After 48 weeks 58% of the patients taking fosamprenavir twice daily had less than 400 copies of viral RNA/mL. However, 61% of the patients taking lopinavir with ritonavir had the same response. It is therefore uncertain that the fosamprenavir regimens are as effective as lopinavir with ritonavir.

The adverse effects and interactions of fosamprenavir are the same as those of amprenavir. Gastrointestinal symptoms and skin rashes are common. As fosamprenavir is metabolised by P450 3A4 it must not be prescribed with drugs such as ergot derivatives, midazolam or triazolam. Fosamprenavir can also interact with complementary medicines such as St John's wort.

Although the pharmacology of fosamprenavir may be an advance on amprenavir, there is currently no evidence to show this will improve the clinical outcomes for patients. Fosamprenavir is only approved for use in combination with ritonavir.

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Ketotifen hydrogen fumarate

Zaditen (Novartis)

250 microgram/mL in 5 mL bottles

Approved indication: seasonal allergic conjunctivitis

Australian Medicines Handbook section 11.3

Ketotifen is an antihistamine which has been available overseas for many years. In addition to antagonising the H₁ histamine receptors, ketotifen stabilises mast cells to prevent the release of inflammatory mediators.

Patients instil ketotifen eye drops two or three times a day. It is unclear how much of the drug is absorbed, but a therapeutic effect begins within a few minutes.

An Australian study compared ketotifen with placebo and levocabastine for one month. Although only half of the 109 patients given ketotifen responded, this was higher than the 41% response in the levocabastine group and significantly better than the 33% response in the placebo group.¹

Olopatadine is another antihistamine which stabilises mast cells. Some comparisons favour olopatadine² while others favour ketotifen.³ There appear to be no published comparisons of ketotifen and ophthalmic non-steroidal anti-inflammatory drugs.

The main adverse events in trials of ketotifen were conjunctival injection, headaches and rhinitis. Patients may also complain of burning or stinging in their eyes.

Although the mast cell stabilisers cromoglycate and lodoxamide can be used to prevent allergic conjunctivitis, they have to be given for a few weeks in advance of exposure to the allergen. Ketotifen is more suited to be one of the options for the short-term treatment of patients with symptoms of seasonal allergic conjunctivitis.

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Pemetrexed disodium

Alimta (Eli Lilly)

vials containing 500 mg powder for reconstitution

Approved indications: lung cancer, mesothelioma

Australian Medicines Handbook section 14.3

Pemetrexed disodium is an antifolate anticancer drug. It inhibits folate-dependent enzymes and inside cells it is converted to a metabolite which is a more potent inhibitor. Inhibiting the enzymes decreases the synthesis of nucleic acids and therefore reduces cell replication.

Although the use of chemotherapy for non-small cell lung cancer is increasing¹, the prognosis remains grim. Pemetrexed

has therefore been studied in patients with metastatic or locally advanced disease which has progressed despite previous chemotherapy. In a phase II study 79 patients were given an infusion of pemetrexed every 21 days. One patient had a complete response and six had partial responses. Although most of the responses occurred in patients who had not been previously treated with platinum-based chemotherapy, they did not live longer. Their median survival was four months, while patients who had already been treated with platinum-based chemotherapy had a median survival of 6.4 months.² The Australian approval of pemetrexed is limited to patients who have previously received platinum-based chemotherapy.

A phase III study randomised 283 patients with advanced non-small cell lung cancer to receive pemetrexed and 288 to receive docetaxel. The overall response rate was about 9% for both drugs, but pemetrexed appeared to be less toxic. The median survival time for each treatment group was approximately eight months.³

Pemetrexed has also been studied in patients with malignant pleural mesothelioma. As only a minority of patients can be treated with surgical resection, there is interest in assessing if chemotherapy has any benefits. In a trial involving 448 patients, pemetrexed and cisplatin were compared with cisplatin alone. As judged by computed tomography, there was a response to treatment in 16.7% of the patients given cisplatin and 41.3% of those given cisplatin and pemetrexed. The median survival with the combination was 12.1 months compared with 9.3 months for cisplatin alone.⁴

Like many anticancer drugs pemetrexed can cause serious adverse reactions, particularly myelosuppression. During the mesothelioma study there were several deaths at the start of the trial. Thereafter, all the patients enrolling in the study were given supplements of folic acid and vitamin B₁₂ to try and reduce the toxicity of pemetrexed. Despite supplements, the combination of cisplatin and pemetrexed will cause neutropenia and leucopenia in 55–60% of patients, so there is a risk of infections and febrile neutropenia. Anaemia and thrombocytopenia are also common, so regular blood tests are needed to check if the patients are still fit for treatment. Although adverse reactions are less frequent when pemetrexed is used alone, supplements are still required. As skin rashes are very common, patients also require premedication with dexamethasone. Non-steroidal anti-inflammatory drugs should not be used with pemetrexed, particularly if renal function is impaired.

While pemetrexed has comparable efficacy to other drugs, such as docetaxel, its benefit to the patient dying of non-small cell lung cancer is less clear. Its effect on quality of life in the phase II study is difficult to interpret, partly because the median number of treatment cycles was only two.² There was no significant difference between pemetrexed and docetaxel in the quality of life analysis of the phase III study.³

Although pemetrexed and cisplatin had an overall advantage in mesothelioma, the choice of cisplatin for the single blind comparative study can be questioned: cisplatin may be an ineffective comparator. In addition, the survival advantage of combination treatment was only of borderline statistical significance ($p = 0.051$) in patients who followed the recommended regimen of cisplatin and pemetrexed with supplements of vitamin B₁₂ and folic acid.⁴

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Ropinirole hydrochloride

Repreve (GlaxoSmithKline)

0.25 mg, 0.5 mg and 2 mg film-coated tablets

Approved indication: restless legs syndrome

Australian Medicines Handbook section 16.2

Patients with restless legs syndrome are distressed by an irresistible urge to move their legs. They may also complain of crawling or burning sensations in their lower limbs. The symptoms are worst at night. In most cases there is no obvious cause, but patients may get relief with self-help techniques such as relaxation exercises.

As restless legs syndrome involves motor restlessness it follows that drugs for Parkinson's disease could have some effect. As levodopa can make the problem worse, there has been interest in dopamine agonists such as bromocriptine and pergolide. Ropinirole is a dopamine agonist which binds to the D₂, D₃ and D₄ receptors and has been used to treat Parkinson's disease. In a crossover study of 22 patients with restless legs syndrome, ropinirole produced more relief than placebo. The main difference between ropinirole and placebo was 12 points on a rating scale of 0–40 points.¹ Larger studies show that after 12 weeks of treatment ropinirole will reduce a patient's score by 11 points while a placebo will reduce it by approximately 8.5 points.

If a patient's restless legs are so frequent and distressing that drug treatment is required then ropinirole can be considered.

It is taken once a day before bedtime and the dose is gradually increased over several weeks according to the patient's response.

The tablets are rapidly absorbed, but first-pass metabolism reduces the bioavailability to 46%. Ropinirole is metabolised in the liver and there is a potential for interactions with drugs, such as theophylline, ciprofloxacin and fluvoxamine, that are metabolised by or inhibit cytochrome P450 1A2. The drug has a half-life of six hours with most of the metabolites being excreted in the urine.

As dopamine receptors are not confined to the central nervous system, some of the adverse effects of ropinirole can be predicted. For example, peripheral dopaminergic effects can cause hypotension. Ropinirole should therefore be used cautiously in patients with cardiovascular disease. Nausea is the most frequent adverse reaction, affecting up to 38% of patients. Ropinirole can cause fatigue and some patients may suddenly fall asleep. Patients with somnolence are advised not to drive or operate machinery. Other adverse effects include dizziness, vomiting and nervousness.

Although some of the benefits of ropinirole could possibly be related to making people sleepy, it seems to have an advantage over placebo. There appear to be no direct comparisons of ropinirole with other dopamine agonists.

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* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

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