policy, PHARM undertook extensive consultation with general practitioners and other stakeholders. By March 1998, persistent and persuasive pressure led to the establishment of the National Prescribing Service (NPS), funded through the federal budget but with an independent board and constitution. The NPS has vigorously set about working with divisions of general practice (it has contracts with two-thirds of them) and has established its credentials through programs to support quality prescribing and use of medicines. The NPS has also pursued some long-hoped for initiatives to promote the quality use of medicines such as a national Therapeutic Advice and Information Service for health professionals. A nationwide Consumer Medicine Information Service is also close to being established.

An important part of the QUM policy is the production of professional drug information independent of industry sponsorship. Financial support was given to a joint venture to produce the *Australian Medicines Handbook* (www.amh.net.au). This reference, covering all pharmaceuticals marketed in Australia, has filled an essential gap. It complements *Australian Prescriber*, the national journal of therapeutics, and the *Therapeutic Guidelines* (www.tg.com.au) series. We are fortunate indeed in having these excellent resources. Finding time to use them, in a busy workplace, remains an issue, although information technology now makes them more readily accessible.

Ten years on, information technology has a greater role in encouraging the quality use of medicines in primary care through the use of electronic medical records and prescribing systems. An important step came earlier this year, with the requirement that the patient's Medicare number be recorded when a prescription is dispensed. Setting up electronic systems and solving the problems associated with them will take much energy in the next few years. It will take time before anticipated benefits flow.

What of the future? Continuation of government funding for the NPS promises that the social marketing of quality initiatives can be consolidated. A new prescribing course for medical schools developed by the NPS and universities is close to completion and will start to have an impact. QUM in pharmacy education will surely spread more widely. Collaboration between patients, pharmacists and doctors to manage multiple medication use is just beginning. In the information age, consumers and professionals already have access to more information and more marketing and promotion than ever before – will this lead to better health outcomes or just quality use of more medicines? A key research question will be to test whether better use of medicines achieves better health outcomes.

Partnership is at the heart of QUM and is likely to come under strain as society counts the cost of new and more expensive drugs. Looking back to see how much has been achieved encourages us to keep working at that partnership so as to minimise the harm and maximise the benefits from the use of pharmaceuticals. Much is at stake.

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Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Prevention of deep vein thrombosis

Editor, – I refer to G. Weisz' recent letter 'Economy class syndrome' (Aust Prescr 2001;24:52). My understanding is that a recent meta-analysis demonstrated no value in the use of aspirin for venous thromboembolism as prophylaxis and treatment, and a reported 3% chance of some degree of gastrointestinal bleeding. It would seem that the use of this drug is best left to the management of arterial problems. Recommendation as a therapy for prevention of deep vein thrombosis is not supported by the *Australian Medicines Handbook* ('Aspirin is probably ineffective in the prevention of venous thromboembolism'), and in view of the incidence of adverse effects I would not advise its use for this purpose.

I would be interested to learn of any studies which support the view that there is a place for aspirin in this setting, or indeed in any situation with a recognised risk of venous thrombosis.

Ashley Collard
General Practitioner
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Agnes Vitry, Senior Editor, Australian Medicines Handbook, comments:

A recent editorial in the *Medical Journal of Australia* concluded that the evidence on the risk of venous thromboembolism associated with air travel was, as yet, missing.[1] Most of the evidence comes from case series and

two conflicting prospective case-control studies.[2,3] Given the current uncertainty about possible increased risk, it seems common sense and harmless to give the usual advice about regular foot exercises, generous fluid intake and avoiding excessive alcohol. A recent randomised trial showed that compression stockings may prevent symptomless deep venous thrombosis but may cause superficial thrombophlebitis in varicose veins.[4]

The second edition of the *Australian Medicines Handbook* did not recommend the use of aspirin for prevention of venous thromboembolism on the basis of a meta-analysis, which suggested aspirin provided relatively little protection for postoperative patients compared to heparins or oral anticoagulants.[5] A recent large trial showed that aspirin (160 mg daily, started before surgery and continued for five weeks) slightly reduced the risk of pulmonary embolism and deep venous thrombosis, but not the overall mortality in patients with hip fracture.[6] Results of this trial are difficult to interpret, as only some of the patients received additional prophylaxis with heparin or low molecular weight heparins, and also as aspirin has not been directly compared with these first-line treatments.

Low-dose aspirin may be used in addition to first-line treatments in patients with hip fracture at low risk of bleeding. At present, low-dose aspirin cannot be recommended for the prevention of venous thromboembolism in other situations.

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Medications which may lower seizure threshold

Editor, – I would like to offer another explanation for the apparent 'seizure activity' reported by Dr Loadsman (Aust Prescr 2001;24:51–2) when pethidine and tramadol were used concurrently. Both these drugs have serotonin reuptake inhibitor activity and have been implicated in serotonin toxicity when combined with other serotonergic drugs. Co-administration of pethidine and tramadol could certainly result in a pharmacodynamic interaction, leading to signs and symptoms of excess serotonin in the central nervous system such as 'twitching and anxiety'. These as well as the neuromuscular features, myoclonic spasms, tremor, clonus, hyperreflexia and hypertonia are included in Sternbach's diagnostic criteria for 'serotonin syndrome' and can easily be mistaken for 'seizure activity'. Physicians should be alert to the possibility of serotonin toxicity when pethidine is given to patients who have recently taken, or are still taking, serotonergic drugs (such as selective serotonin reuptake inhibitors and monoamine oxidase inhibitors). Concurrent use of pethidine and tramadol should be undertaken with caution or avoided when possible, because of the risk of serotonin toxicity.

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Oxaliplatin

Editor, – The new drug comment (Aust Prescr 2001;24:73–4) does not reflect the Australian trial experience with oxaliplatin. At the American Society of Clinical Oncology meeting in San Francisco we reported a phase II trial of oxaliplatin in conjunction with 5-fluorouracil and folinic acid in 40 patients with previously untreated advanced or metastatic colorectal cancer.[1] There was a low rate of severe (grade 3/4) toxicities and these included neuropathy (grade 3–17%), diarrhoea (grade 3–11%), mucositis (grade 3–4%) and neutropenia (grade 3/4–34%). Nausea and vomiting were not a major problem with the use of simple antiemetics. In addition the tumour response rate was 56% (95% CI 38–72%), which is very high for these conditions.

The comment that 'like other platinum-based drugs, oxaliplatin is very toxic' is therefore inaccurate, as is the following suggestion that 'most patients will have vomiting, diarrhoea, anaemia and altered liver function tests'. These comments cannot have been written by anyone who has ever used this compound.

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Editorial comment

The Executive Editorial Board prepared the new drug comment before oxaliplatin was marketed in Australia. Prior to marketing there is obviously little information available about the use of any new drug in Australia. To ensure readers are presented with a balanced view of a new drug the Executive Editorial Board considers data from a variety of sources including information provided by the manufacturer. While the Executive Editorial Board is interested in the results of Dr Clarke's phase II study they do not negate the new drug comment.

The comment was based on the pivotal clinical trials which used different regimens from the phase II study. In these trials symptoms of neuropathy developed in 85–95% of patients. Anaemia occurred in more than 80% of patients and neutropenia and thrombocytopenia were very common. The comment that most patients will have vomiting and diarrhoea is also consistent with the manufacturer's product information.

In Dr Clarke's trial 83% of the patients required a dose reduction and toxicity resulted in 25% ceasing treatment. While the frequency of severe adverse effects may be low from an oncology perspective, it is important that patients decide what is acceptable to them. The Executive Editorial Board hopes that the favourable response rate seen in the trial will lead to improved survival for the patients.

Medicinal mishap

Statin-fibrate combination therapy

Prepared by Ian Hamilton-Craig, Senior Visiting Cardiologist, Repatriation General Hospital, Adelaide, and David Miller, Senior Visiting Nephrologist, Flinders Medical Centre, Adelaide

Case 1

After coronary bypass five years ago this patient was treated with atorvastatin 40 mg daily and gemfibrozil 600 mg twice daily for combined hyperlipidaemia. He also took extended-release diltiazem for hypertension and aspirin 100 mg daily. He complained of minor, tolerable muscle aches but his creatine kinase levels were normal.

In March, cerivastatin 0.3 mg daily was substituted for atorvastatin. Three weeks later, the patient noticed flu-like symptoms with aching of the neck, shoulders and limbs. He persisted with his therapy in spite of severe muscle aching and stiffness, weakness, lethargy and decreasing urinary output. When he presented in April he had signs of acute renal failure and his urine contained pigmented casts typical of myoglobinuria. His creatine kinase peaked at over 30 000 U/L with a high creatinine (0.75 mmol/L) and urea (49.7 mmol/L). His liver function was also affected (LDH 2727 U/L, ALT 1089 U/L, AST 1827 U/L). After haemodialysis for 15 days, his initially profound muscle weakness improved and his strength returned to normal over subsequent weeks, as did his renal function.

Case 2

A 63-year-old woman with combined hyperlipidaemia (total cholesterol 7.5 mmol/L, triglycerides 10.2 mmol/L) was prescribed cerivastatin 0.4 mg daily. Three years previously she had been treated with atorvastatin, but ceased this after six months because of severe muscle aches and pains. Gemfibrozil 600 mg daily was subsequently added to cerivastatin when her total cholesterol and triglycerides were 5.4 and 5.7 mmol/L respectively. Three weeks later, she developed stiffness and pain in the lower back, with severe impairment of mobility. She ceased medications and her symptoms had largely resolved on presentation two days later. Her plasma concentrations were: creatine kinase 14 500 U/L, LDH 647 U/L, AST 352 U/L, ALT 191 U/L. Glucose, creatinine and urea concentrations were normal. TSH was marginally elevated (4.7 mIU/L) and free T4 borderline (11 pmol/L). Two days later her creatine kinase was 45 600 U/L. Her symptoms and creatine kinase concentrations were normal one week later.

Comment

Rhabdomyolysis has been a frequent adverse drug reaction with cerivastatin-gemfibrozil combination therapy. Fatalities have led to the withdrawal of cerivastatin from the market, other than in Japan where gemfibrozil is not available.

High plasma concentrations of 'statins' predispose to rhabdomyolysis with either high doses or co-administration of cytochrome P450 inhibitors, including calcium channel blockers[1] (see Case 1).

Conditions predisposing to myopathy include severe hypoxia, hyperthermia, hypotension, hypothyroidism (see Case 2), recent major surgery, severe acute infections, severe endocrine, metabolic and electrolyte disturbances, uncontrolled seizures and possibly underlying genetic myopathies.[2] Patients experiencing myopathy with one statin are likely to experience it with another (see Cases 1 and 2).

Severe myopathy may occur without elevation of creatine kinase, and therapy should be withdrawn in patients, especially elderly women, complaining of muscle weakness.[3] Patients should have normal thyroid function before starting treatment with lipid-lowering therapy. Adverse drug reactions should be reported to the Adverse Drug Reactions Advisory Committee to ensure adequate post-marketing surveillance.

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Muscle disorders with statins – to August 2001

Statin	*Total number of reports*	*Reports of myalgia, myopathy and myositis (% of total)*	*Reports of rhabdomyolysis (% of total)*
Cerivastatin	148	68 (45.9%)	27 (18.2%)
as monotherapy			7 (4.7%)
with gemfibrozil			20 (13.5%)
Simvastatin	2248	427 (19.0%)	32 (1.4%)
Atorvastatin	679	130 (19.1%)	3 (0.4%)
Pravastatin	339	85 (25.1%)	3 (0.9%)
Fluvastatin	242	62 (25.6%)	1 (0.4%)

Table provided by Adverse Drug Reactions Advisory Committee