

4. Thompson WG. Irritable bowel syndrome: a management strategy. *Baillieres Best Pract Res Clin Gastroenterol* 1999;13:453-60.
5. Pandolfino JE, Howden CW, Kahrilas PJ. Motility modifying agents and management of disorders of gastrointestinal motility. *Gastroenterology* 2000;118(2 Suppl 1):S32-S47.
6. Poynard T, Naveau S, Mory B, Chaput JC. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;8:499-510.
7. Gershon MD. Roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 1999;13(Suppl 2):15-30.

Dr Fraser is currently involved in a multicentre trial of irritable bowel syndrome treatment (tegaserod).

Self-test questions

The following statements are either true or false (answers on page 75)

9. Some patients with irritable bowel syndrome do not experience abdominal pain.
10. Up to half the patients with irritable bowel syndrome have clinical features of depression.

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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Buprenorphine

Subutex (Reckitt Benckiser)

0.4 mg, 2 mg and 8 mg sublingual tablets

Approved indication: opiate dependence

Australian Medicines Handbook Section 18.6.3

Buprenorphine is a partial agonist of opioid receptors. The drug has been used, at low doses (0.2 mg), as a sublingual analgesic. Higher doses have now been approved for the treatment of opiate dependence. Buprenorphine can be used in detoxification or as a maintenance treatment. Its action on the receptors reduces the cravings for opioid drugs.

The drug is taken sublingually because of the first-pass metabolism which follows an oral dose. Even when given sublingually, the tablets only have a bioavailability of 30–35%. Buprenorphine is metabolised by the cytochrome P450 system. As CYP3A4 is involved, inhibitors of this enzyme, such as macrolide antibiotics, have the potential to increase concentrations of buprenorphine. Most of the metabolites are excreted in the bile. As buprenorphine has a mean half-life of 35 hours it is feasible to give some patients less than daily dosing.

A randomised trial has compared the efficacy of buprenorphine with that of clonidine and naltrexone in 162 patients undergoing detoxification. The detoxification was successfully completed by 65% of the patients given clonidine, 81% of those given clonidine and naltrexone, and 81% of those given buprenorphine.¹ The Cochrane Collaboration has reviewed the evidence supporting buprenorphine in the management of opioid withdrawal, but has not reached a firm conclusion.²

For maintenance treatment, buprenorphine should be taken at least six hours after the last dose of heroin. This is to reduce the risk of triggering withdrawal symptoms. For patients transferring from methadone there should be a delay of at least 24 hours before starting buprenorphine. Treatment begins with a 4 mg dose which is increased according to the patient's

response. The maximum dose is 32 mg a day. Once the patient is stable the dose frequency can be reduced. Some patients will manage with three doses a week.

Buprenorphine has been compared with methadone. One trial studied 72 patients for six months. While more patients taking methadone were retained in treatment, both treatments worked well. Urine tests showed reduced opioid use; 60% of the tests were negative for patients taking buprenorphine compared to 66% of the tests from patients taking methadone.³

A major problem with buprenorphine is the risk of abuse. As patients given buprenorphine for pain can become addicted it is clear that it can cause dependence. Some patients grind up the tablets so that they can inject the drug. This is dangerous, particularly if the patient is also using benzodiazepines. Deaths have occurred from cardiorespiratory depression when buprenorphine and benzodiazepines have been injected.

Other adverse effects are difficult to identify as the adverse reactions reported in clinical trials may be due to withdrawal or opioid toxicity. Symptoms reported include headache, abdominal pain, chills, insomnia, nausea, vomiting and diarrhoea. Liver function may be altered and some patients will develop hepatitis.

If a decision is made to cease treatment, buprenorphine should not be stopped suddenly. A gradual reduction of the dose over three weeks is recommended.

Buprenorphine has been used to treat drug addiction in France since 1996. *Australian Prescriber's* sister journal *La Revue Prescrire* has reviewed its use and found it to be an effective treatment. The French experience confirms that the main risks of buprenorphine are linked to misuse. They recommend that there should be good communication between the prescribing doctor and the pharmacist, particularly about how many tablets to dispense at a time. Using buprenorphine as one part of a co-ordinated medical and psychosocial treatment program is also important.⁴

REFERENCES

1. O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR, Rounsaville BJ. Three methods of opioid detoxification in a primary care setting. *Ann Intern Med* 1997;127:526-30.
2. Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2000. Oxford: Update Software.
3. Pani PP, Maremmani I, Pirastu R, Tagliamonte A, Gessa GL. Buprenorphine: A controlled clinical trial in the treatment of opioid dependence. *Drug Alcohol Depend* 2000;60:39-50.
4. Buprenorphine replacement therapy. *Prescrire International* 1999;8:124-7.

Exemestane

Aromasin (Pharmacia & Upjohn)

25 mg tablets

Approved indication: advanced breast cancer

Australian Medicines Handbook Section 17.10.2

Oestrogen can stimulate the proliferation of breast cancer cells. The main source of oestrogen in postmenopausal women is the conversion of androgens from the adrenal glands. This conversion can be blocked by inhibiting the aromatase enzyme. Exemestane is an aromatase inhibitor. Unlike other aromatase inhibitors, such as aminoglutethimide, anastrozole and letrozole, exemestane has a steroidal structure.

A single dose of exemestane suppresses oestrogen concentrations by 90%. Each dose is well absorbed but the bioavailability is reduced by first-pass metabolism. Patients should take the drug after a meal as this increases plasma concentrations of exemestane by 30–40%. The drug is almost completely metabolised with the metabolites being excreted in the faeces and urine. Clearance is reduced by renal and hepatic impairment.

A double-blind trial has studied exemestane as second-line therapy in postmenopausal women. All the women had breast cancers which had progressed despite treatment with tamoxifen. In this trial 366 women were randomised to take exemestane and 403 took megestrol, a synthetic progestogen with an antitumour action. The objective response rates were 15% for exemestane and 12% for megestrol. This difference is not significant, however exemestane did have some advantages. The median time to progression of the tumour was 20 weeks with exemestane and 17 weeks with megestrol. This contributes to a significantly longer median survival time.¹

Although there have only been uncontrolled phase II studies, exemestane has also been approved as a third-line treatment. Approximately 9% of women, whose tumours have progressed despite multiple hormone therapies, will respond to exemestane. In women with metastatic disease which had progressed after treatment with a non-steroidal aromatase inhibitor, 7% responded to exemestane.²

Only 3% of the women in the clinical trials had to withdraw because of adverse events. Compared to megestrol, exemestane caused more hot flushes, headaches, rashes, nausea and vomiting.

Exemestane is at least as effective as megestrol, but it has not been compared with other aromatase inhibitors as second-line therapy. As most of the women in the comparative trial¹ had hormone-receptor positive tumours, the efficacy of exemestane in oestrogen-receptor negative tumours is uncertain.

REFERENCES

1. The Exemestane Study Group. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. *J Clin Oncol* 2000;18:1399-411.
2. Lønning PE, Bajetta E, Murray R, Tubiana-Hulin M, Eisenberg PD, Mickiewicz E, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol* 2000;18:2234-44.

Gadoversetamide

OptiMARK (Mallinckrodt)

0.5 mmol/mL solution in 10 mL, 15 mL, 20 mL or 30 mL pre-filled syringes and vials containing 5 mL, 10 mL, 15 mL or 20 mL

Approved indication: magnetic resonance imaging

Gadoversetamide is an injectable contrast medium. It can enhance the signal intensity during magnetic resonance imaging (MRI) of intracranial and spinal lesions when the blood-brain barrier is abnormal. The medium can also be used when imaging the liver.

An injection of gadoversetamide is given not more than an hour before the MRI. The medium is distributed into the extracellular fluid space. Most of the dose is excreted unchanged in the urine within 24 hours.

Clinical trials have compared gadoversetamide with gadopentetate dimeglumine, another gadolinium-containing medium. The image enhancement was considered to be equivalent.

Approximately 30% of patients experience an adverse effect after receiving gadoversetamide. They may complain of headache, altered taste, dizziness and nausea. The use of this contrast medium has not been studied in patients with renal impairment.

Gatifloxacin

Tequin, Tequin IV (Bristol-Myers Squibb)

400 mg film-coated tablets

infusion bags containing 400 mg/200 mL

Approved indication: specified infections

Australian Medicines Handbook Section 5.1.12

Gatifloxacin is a fluoroquinolone antibiotic with a wide range of activity. It is active against aerobic gram-positive and gram-negative bacteria, and also *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae*. This makes gatifloxacin suitable for the treatment of respiratory infections such as community-acquired pneumonia.

In patients with community-acquired pneumonia, gatifloxacin is as effective as clarithromycin and ceftriaxone. However, these drugs are not usually the first-line therapy in Australia. Gatifloxacin has also not been compared with first-line drugs for acute exacerbations of chronic bronchitis, but it is as effective as cefuroxime for this indication.

The antibacterial activity of fluoroquinolones includes *Neisseria gonorrhoeae*. Gatifloxacin can therefore be used to

treat uncomplicated urethral, pharyngeal and rectal gonorrhoea in men and endocervical, pharyngeal and rectal gonorrhoea in women.

Gatifloxacin has a half-life of 7–14 hours and is given once a day. It is well absorbed with the result that the oral formulation has similar pharmacokinetics to the intravenous formulation. The concentration of the drug in some target organs, e.g. lung parenchyma, is greater than the serum concentration. Most of the dose is excreted unchanged in the urine, so an adjustment is needed if the patient has renal impairment.

Dysuria and haematuria are adverse effects, but more common problems include nausea, vomiting, diarrhoea and vaginitis. As gatifloxacin may prolong the QT_c interval it should be avoided in patients with hypokalaemia and in those taking drugs such as tricyclic antidepressants. Gatifloxacin can also alter blood glucose concentrations and may increase the risk of patients being treated for diabetes developing hypoglycaemia.

Like other fluoroquinolones, gatifloxacin should be kept in reserve, for occasions when a cheaper drug is not effective.

Glimepiride

Amaryl (Aventis)

1 mg, 2 mg and 4 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook Section 10.1.2

When non-insulin dependent diabetics fail to respond to weight loss and dietary modification, oral antidiabetic drugs can be added to their management. Glimepiride adds to the choice of sulfonylurea drugs for these patients. It was approved in 1996 but has only recently been marketed.

The dose of glimepiride must be titrated for each patient, depending on blood glucose measurements. Treatment begins with 1 mg daily and is increased by 1 mg every 1–2 weeks. Most patients will be controlled with a dose of 4 mg or less. If higher doses are needed, there may be a benefit in dividing the dose. The maximum dose is 8 mg daily.

Usually glimepiride will be taken before breakfast. It is completely absorbed and reaches a maximum concentration within three hours. Glimepiride is completely metabolised and has a half-life of 5–8 hours. The main metabolite also has some antidiabetic effect, so, overall, the hypoglycaemic action of a single dose lasts for 24 hours. Most of the metabolites are excreted in the urine, so the drug is contraindicated in patients with severe impairment of renal or hepatic function.

Like other sulfonylureas, glimepiride releases insulin from the pancreas. This can cause hypoglycaemia, particularly in the first month of treatment. Patients and their carers should be informed about the risks of hypoglycaemia as part of their diabetes education. The most common adverse reactions, occurring in 1–2% of patients, are gastrointestinal. Many drugs may affect the hypoglycaemic action of glimepiride.

Although less is known about its long-term safety, glimepiride is probably as effective as glibenclamide when a long-acting sulfonylurea is indicated.

Mirtazapine

Remeron (Organon)

Avanza (British Pharmaceuticals)

30 mg tablets

Approved indication: major depression

Australian Medicines Handbook Section 18.1

Mirtazapine is a tetracyclic antidepressant which was approved for marketing back in 1996. By antagonising central adrenoceptors, mirtazapine increases the release of noradrenaline and serotonin. As mirtazapine blocks 5HT₂ and 5HT₃ receptors, the serotonin acts at 5HT₁ receptors.¹

The tablets have a bioavailability of 50% and peak plasma concentrations are reached two hours after a dose. Mirtazapine is extensively metabolised and has an average half-life of 20–40 hours. It is suitable for once daily dosing with a steady state being reached in three or four days. Clearance may be reduced by hepatic or renal impairment.

Treatment begins with 15 mg daily. If there is no response within 2–4 weeks, the dose can be increased. If there is no response to the maximum dose of 45 mg, treatment should be stopped.

Several studies, many of them of only a few weeks' duration, have compared mirtazapine to placebo. Overall, mirtazapine is more effective. It has also been compared to other antidepressants. Most of these studies found the efficacy of mirtazapine to be statistically equivalent to amitriptyline, clomipramine, doxepin and trazodone. There are two published studies which suggest that mirtazapine has similar effects to fluoxetine and citalopram.

Mirtazapine is better tolerated than amitriptyline. Drowsiness can occur in the first few weeks of treatment and does not respond to reducing the dose. Other adverse effects include altered liver enzymes, bone marrow depression, oedema and weight gain. Although mirtazapine has weak anticholinergic activity, caution is advised when prescribing to patients with glaucoma or those at risk of urinary retention.

Mirtazapine may potentiate the effects of alcohol and benzodiazepines. The drug should not be prescribed with, or within two weeks of ceasing, a monoamine oxidase inhibitor.

REFERENCE

1. Mylecharane EJ. Serotonin receptor agonists and antagonists—mechanisms of action. *Aust Prescr* 1991;14:46-9.

Oxaliplatin

Eloxatin (Sanofi-Synthelabo)

vials containing 50 mg or 100 mg as lyophilised powder

Approved indication: colorectal cancer

Australian Medicines Handbook Section 14.1

Metastatic colorectal cancer has a poor prognosis. Only about 5% of patients will survive for five years, but their chances may be improved with chemotherapy. Regimens containing 5-fluorouracil and calcium folinate have an established role in therapy.

Oxaliplatin is an analogue of platinum. It has a wide spectrum of cytotoxicity and is active against tumours which are usually insensitive to platinum. Although oxaliplatin has been studied as monotherapy for colorectal cancer, it has been approved for use in combination with 5-fluorouracil and calcium folinate. Most studies have involved regimens with continuous infusion of 5-fluorouracil. Oxaliplatin is given as a 2–6 hour infusion every two or three weeks. After two hours only 15% of the platinum is present in the circulation and no intact oxaliplatin remains. The platinum is distributed to the tissues and binds irreversibly to red blood cells. Most of the platinum is eliminated in the urine with approximately half the dose being excreted within five days. Renal impairment reduces clearance.

One clinical trial compared the efficacy of 5-fluorouracil and calcium folinate with or without oxaliplatin in 200 patients with previously untreated metastatic colorectal cancer. Treatment was repeated every three weeks. There was an objective response in 34% of the patients who received oxaliplatin and 12% in those who did not. The median progression-free survival was 8.3 months as opposed to 4.2 months.¹ Although these results favour oxaliplatin, there was no improvement in survival and oxaliplatin's approval has now been restricted to patients whose cancer has progressed. A study of oxaliplatin as second-line therapy included 97 patients whose disease had progressed despite treatment with 5-fluorouracil and calcium folinate. These patients only have a few months to live, but adding oxaliplatin to the regimen induced a response in 20 patients. The patients had a median survival time of 11 months.

Like other platinum-based drugs, oxaliplatin is very toxic. Most patients will have vomiting, diarrhoea, anaemia and altered liver function tests. The incidence of adverse effects increases when oxaliplatin is added to 5-fluorouracil and calcium folinate. Treatment is limited by neurotoxicity. Up to 95% of patients will develop a peripheral neuropathy.

Adding oxaliplatin as second-line therapy results in a median progression-free survival of 4.7 months. Patients and their doctors will have to decide if this outcome is offset by the toxicity of treatment.

REFERENCE

1. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;18:136-47.

Pneumococcal conjugate vaccine

Prevenar (Wyeth)

0.5 mL single dose vials

Approved indication: immunisation

Australian Medicines Handbook Section 20.1

The currently available pneumococcal vaccine contains a mixture of polysaccharides from the 23 most prevalent serotypes of pneumococcus. Although the vaccine is recommended for people at high risk of pneumococcal disease,

it is not very immunogenic in infants and is not recommended for children under two years old. The new vaccine only contains polysaccharides from seven serotypes, but it is conjugated to a diphtheria protein. This provokes an immune response in infants, so the vaccine can be used to immunise children between six weeks and nine years of age.

If immunisation begins at six to eight weeks of age the infant needs three intramuscular injections at least four weeks apart, followed by a booster injection before the age of two. Children who are one to two years old need two injections, but children over two years old need only a single dose.

Although older children require only one injection they are more likely to react to it. Soreness at the injection site occurs in nearly 60% of cases and in 20% this interferes with limb movement. Fever, irritability and vomiting are other very common adverse effects. Reactions are more likely if the child is being simultaneously immunised with pertussis vaccine.

Although 51–90% of children will develop an antibody concentration of 1.0 microgram/mL after three doses, the minimum protective concentration is unknown. A large trial in the USA found the efficacy of the vaccine was 87% against pneumonia caused by pneumococci from the same serotypes as used in the vaccine. There was also a 9% reduction in visits to the doctor for otitis media.¹

The American Academy of Pediatrics has recommended that all children, 23 months and younger, be given the vaccine with their routine immunisations.² Australia is more likely to opt for protecting high-risk groups rather than universal immunisation. The Australian Standard Vaccination Schedule already requires multiple immunisations. In addition to the extra injections it is not clear how the new vaccine will interact with some of the combined vaccines used in Australia. While the vaccine may help to reduce the significant morbidity of pneumococcal disease in Aboriginal children, there is little information about its use in indigenous peoples. The pneumococcal serotypes used in the vaccine may differ from those which cause disease in central Australia.

REFERENCES

1. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000;19:187-95.
2. American Academy of Pediatrics. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics* 2000;106:362-6.

Recombinant factor IX

Benefix (Wyeth)

vials containing 250 IU, 500 IU and 1000 IU as lyophilised powder

Approved indication: haemophilia B

Australian Medicines Handbook Section 7.4

Factor IX is part of the intrinsic pathway of coagulation. Approximately one boy in 100 000 is born with a deficiency or dysfunction of factor IX (haemophilia B).

If someone with a factor IX deficiency develops bleeding, they can be treated with plasma concentrates derived from blood donations. There is always a small risk of a blood-borne infection being transmitted in these products. In addition some of the concentrates are enriched with prothrombin and can cause thromboembolism. A recombinant factor IX should avoid these problems.

Patients switched to the recombinant factor IX may need to be given a higher dose than would be needed with a plasma-derived product. An assay should be used to ensure the correct level of factor IX activity is reached.

As haemophilia B is a rare disease clinical trials have only included 108 patients. In addition to the treatment of bleeding, recombinant factor IX has also been used successfully to prevent bleeding during surgery.

In the clinical trials the slow injection of factor IX could cause headache, fevers, chills, nausea and vomiting. Prescribers must be ready to deal with acute hypersensitivity reactions. Allergic reactions may be more frequent in patients who have developed inhibitors (neutralising antibodies) to factor IX products.

NEW FORMULATION

Nedocromil sodium

Tilade CFC-Free (Aventis Pharma)
2 mg/actuation metered dose inhaler

NEW STRENGTHS

Epoetin alfa (rch)

Epex (Janssen-Cilag)
5000 IU/0.5 mL, 6000 IU/0.6 mL, 7000 IU/0.7 mL,
8000 IU/0.8 mL and 9000 IU/0.9 mL

Etoposide

Etopophos (Bristol-Myers Squibb)
113.6 mg and 1136 mg lyophilised powder

Oxycodone

OxyNorm (Mundipharma)
10 mg and 20 mg capsules

Answers to self-test questions

1. False	3. False	5. True
2. False	4. True	6. True
7. False	9. False	
8. True	10. True	

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list, contact the Australian Prescriber Mailing Service.

Postal: Australian Prescriber Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

NAME:

ADDRESS:

.....

.....

.....

PROFESSION:

(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist, etc.)

The full text of *Australian Prescriber* is available on the internet, free of charge, at www.australianprescriber.com

Tick whichever of the following apply:

I have access to the *Australian Prescriber* web site on the internet Yes No

Place me on the mailing list

Delete me from the mailing list

My reference number is

Change my address

My reference number is

Send me all the available back issues (from Vol. 22 No. 6, 1999)

Send me the following back issue/s

.....

Editorial office

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6289 7038

Facsimile: (02) 6289 8641

Postal: The Editor
Australian Prescriber
PO Box 100
WODEN ACT 2606
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com