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Australian Prescriber
Volume 24
Number 3
2001

EDITORIAL

Guiding guidelines into practice

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Index words: evidence-based medicine, clinical governance, quality assurance, standards.

(Aust Prescr 2001;24:50–1)

Introduction

Guidelines have been defined as 'systemised statements designed to assist clinicians in managing patients'. However, their use is not always straightforward. They can be used for assisting clinicians with clinical decisions, as standards for determining the quality of care, and as part of wider processes for improving the quality of care. In a perfect world guidelines would be unnecessary, clinicians would obtain the best available evidence relevant to each patient's problems at each point in time, and use it in their practice.

There are disadvantages to the use of guidelines as well as advantages. Before deciding to what extent we should embrace or repel them – let alone how we should do so – it is important first to look at the context in which guidelines are used.

Guidelines and evidence-based medicine

Guidelines are designed to help clinicians do the right thing. However, this means we have to define what 'the right thing' is.

In this issue...

Nine new drugs are discussed in this issue. It will be difficult to assess what role some of them will have in therapy until more information is available. This is where clinical practice guidelines can be helpful, but Chris Del Mar reminds us of some of the problems with guidelines.

It is not only new drugs which can change practice. Con Aroney informs us how new laboratory tests are helping to change the management of acute coronary syndromes.

While there have been no dramatic changes in the management of vaginitis and vulvitis, Gayle Fischer and Graeme Dennerstein stress the importance of an accurate diagnosis in successful treatment. Excluding a serious illness is also important in the management of irritable bowel syndrome, but Rob Fraser tells us that the exact cause of the condition is still unknown.

Depression is another condition which can be misdiagnosed, particularly in the elderly where it may co-exist with other conditions such as dementia. Although depression is common in older age, John Snowdon tells us that the prognosis may be as good as it is in younger patients.

Evidence-based medicine, the process of obtaining and using the best available evidence from research, clearly has a central role although evidence is lacking for many areas of clinical practice. Originally developed as a process to provide the clinician with the information with which to make decisions, it has been seized upon by the makers of guidelines to ensure that their guidelines are optimal. Guidelines are not necessarily evidence-based (in the past, they were often only 'consensus-based'), but the best ones are evidence-based.

Guidelines as standards

What about clinicians who do not adhere to a guideline? Guidelines have changed their function from being something designed to assist clinicians in managing patients, to become a standard. For example, the National Breast Cancer Centre commissioned guidelines for the management of women with a new symptom in the breast. These guidelines were studied not only to decide if they changed doctors' behaviour (they did when the education was combined with an audit), but also as benchmarks to make judgements about the doctors' standard of care.[1] The National Prescribing Service has also encouraged audits of antibiotic prescribing in which guidelines have been used as the standard against which judgements can be made.

Standards can be set at several levels: minimal, normative and exemplary.[2] Each has its own uses. Minimal standards can be used to identify health professionals who perhaps require remedial or even punitive action. Exemplary standards aim to encourage the whole profession to improve. It is clearly important to recognise which level should be applied to any guidelines that will be used as a standard.

Guidelines and quality of care

Guidelines can be used to improve the quality of care. They can help clinicians who want to know what to do. This can be amplified into a wider process such as 'quality assurance', 'quality improvement' and more recently 'clinical governance'. These all involve a cycle of selecting an area of care, measuring this against guidelines as a standard, and then changing management to address any discovered shortcomings. However, the notion of 'guidelines-as-standards' as a means of reducing 'clinical variation' may be flawed.

First, variations in care do not necessarily imply variations in quality. There are many situations in which one form of care is as good as another. A good example comes from the use of antibiotics for acute otitis media.[3] The benefits of antibiotics are marginal and may be counterbalanced by the adverse effects. In other words, symptomatic treatment with or without

a prescription for antibiotics may be equally good quality care.

Secondly, guidelines imply that one size should fit all. In some situations this is likely to be correct. For example, a breast lump in a woman 65 years old needs to be properly investigated in a specialist clinic until malignancy has been excluded. However, there will always be some people who do not fit the guidelines. General practitioners are experts at finding the right treatment for their patients. This involves taking account of their psychosocial factors and welding different pieces of information together to make a decision.[4] A woman might have a phobia of needles that would make fine-needle aspiration of her breast a serious problem; she may also have other more pressing and urgent medical or non-medical problems that assume a greater priority. Being sensitive to these issues may actually be a sign of very good quality care. Patients' views (if well informed) may be as important a factor in deciding what to do as the evidence on which guidelines are based.

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FURTHER READING

Some guidelines can be accessed through the following web sites:

http://www.guideline.gov/ (US National Guidelines clearinghouse)

http://www.health.gov.au/ (Commonwealth Department of Health and Aged Care – a good starting point for several other sites)

http://www.nhmrc.health.gov.au/ (National Health and Medical Research Council)

http://www.healthinsite.gov.au/ (A federally-funded information site about health)

http://www.ctfphc.org/ (One of the best sites on preventive health care, from the Canadian Task Force)

http://www.tg.com.au (Therapeutic Guidelines) (available at cost)

(Note: Three members of the Australian Prescriber Executive Editorial Board, Doctors R.F.W. Moulds, J.W.G. Tiller and J.S. Dowden, are unpaid directors of Therapeutic Guidelines Ltd., a not-for-profit organisation.)

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.

Prescribing by numbers: pharmacoeconomic consideration

Editor, – Referring to comments made by P. Neeskens (Aust Prescr 2000;23:115) on the usefulness of the number needed to treat (NNT), it is worth mentioning that the figures were misquoted. The original article by Eve Hurley (Aust Prescr 2000;23:38) stated that X = event rate control was 4.1% and that Y = event rate active (with gemfibrozil) was 2.7%. In Dr Neeskens' comments these two figures were transposed.

While it may be true that the NNT does not always give a feel of the relevance of an intervention, it certainly does provide a useful measure for comparing interventions when pharmacoeconomic evaluations are performed. From the Helsinki Heart study, it can be calculated that to treat the 71 men for 5 years with gemfibrozil just to prevent one event would cost: 220 (ZAR) x 12 (months) x 71 (men) x 5 (years) = 937 200 ZAR (South African Rands) in drug costs alone. This is equivalent to $220 000. If there is a cost-effective non-pharmacological intervention or an alternative drug that provides the same or similar relative risk reduction (of 34% as quoted) then the use of NNT will help in decision-making for policy-makers as well as clinicians.

N. Malangu
Lecturer
Medunsa School of Pharmacy
South Africa

Medications which may lower seizure threshold

Editor, – Amongst the medications which may lower seizure threshold (Aust Prescr 2001;24:8-9) two stimulant medicines are listed, namely dexamphetamine (uncommon) and methylphenidate (anecdotal reports).

I would like to add another anecdotal report regarding caffeine, a self-medication or perhaps a recreational drug. I have seen two patients within a year or two of each other, both middle-aged women, who gave me almost identical histories. They had each been investigated for the cause of major seizures, including inpatient EEG monitoring, without a cause being found or effective relief obtained. On questioning, they each admitted to being heavy drinkers of instant coffee, to the order of 40 cups a day. I advised both women to reduce their coffee consumption to normal levels, and neither of them has had any further seizures over 10 years.

Michael Grounds
General Practitioner
Bendigo, Vic.

Editor, – I found Professor Neil Buchanan's article 'Medications which may lower seizure threshold' (Aust Prescr 2001;24:8-9) very timely and useful. Over the last month, the Acute Pain Service at my hospital has come across three patients taking pethidine (for patient controlled

analgesia) who have exhibited signs of seizure activity (twitching, anxiety etc.). None actually fitted and none had a previous history of epilepsy.

We see this problem from time to time but not with this sort of frequency. Interestingly, at least two and possibly all of the patients were also on tramadol, a drug with mixed opioid agonist and serotonin/noradrenaline reuptake inhibitor activity. The product information for tramadol suggests that it should be included in Professor Buchanan's list, and perhaps particular caution is required when considering the combined use of tramadol with pethidine.

John Loadsman
Staff Specialist
Department of Anaesthetics
Royal Prince Alfred Hospital
Camperdown, NSW

Economy class syndrome

Editor, – There has recently been a multitude of communications in the media describing 'economy class' syndrome. I believe it is important to know that this disease is not exclusive and can also occur in upper class travellers. They also need prophylactic measures. Here is a brief case history:

A 72-year-old man in good health and without varicose veins flew business class to Sicily. He had a one hour stop in Bangkok and two hours in Rome. On descending in Rome, he felt a 'discomfort in his foot'. Some two days later, a Sicilian doctor diagnosed a deep vein thrombosis. The patient was given daily injections in his 'abdomen' for two weeks to 'thin the blood'. His symptoms soon subsided and on his return to Sydney two months later, no clinical signs remained and sonogram showed free venous flow in the leg.

This case history has justified my policy of handing my patients a small article on the venous circulation and thrombosis before their trip. I advise on hydration and mobilisation of legs, suggest anti-embolism stockings, particularly for women on oral contraceptives and/or hormone replacement therapy, and prescribe low-dose aspirin for two day before and a day after the trip.

George Weisz
Orthopaedic Surgeon
Bondi Junction, NSW

Drug treatment for opioid dependence

Editor, – The author of 'Drug treatment for opioid dependence' (Aust Prescr 2001;24:4-6) refers to the term dependence as if there is only one possible meaning. However, there are two forms of dependence. One is where the opioid receptors require an opioid to prevent withdrawal effects – *physical* dependence – and the other is a *psychological* dependence whereby illicit opioid users use opioids but are not physically dependent. It is acknowledged that most, if not all, physically dependent people would have been psychologically dependent at some stage and may still be so. Which group is the author referring to? Does the author imply that there are 70 000 heroin users that are physically dependent or are some of these users not physically but psychologically dependent?

Our research into methadone reveals a wide and unpredictable half-life ranging from as little as four hours to as long as four days. The author states that methadone for maintenance need only be given once a day. This does not correlate with the variable half-life of methadone and may be one of the reasons that methadone given once a day fails in about 15% of patients. If the half-life is short, it would be possible to treat that person with a large once-daily methadone dose but from a pharmacological perspective they may well do better with a smaller dose given more frequently, more in line with the half-life of methadone. From the practical perspective this equates to twice daily. This approach has been verified when using methadone for pain control.

Associate Professor D.A. Cherry and
Associate Professor G.K. Gourlay
Pain Management Unit
Flinders Medical Centre
Bedford Park, SA

Dr Alex Wodak, author of 'Drug treatment for opioid dependence', comments:

Professors Cherry and Gourlay argue that physical and psychological forms of drug dependence should be considered separately. While contemporary definitions of 'drug dependence' by reputable authorities abound, most now regard the physical and psychological components of drug dependence as inseparable. The operational definitions used today are mainly derived from the DSM-IV and ICD-10 classifications of diseases. The estimate of more than 70 000 severely dependent heroin users in Australia was based on a unitary rather than a dualistic notion of drug dependence.

The wide variation in methadone plasma half-life, rightly emphasised by Professors Cherry and Gourlay, seems more of a problem for analgesia than for the management of heroin dependence. Even if twice-daily administration was preferable for methadone treatment, the need for supervised administration for the vast majority makes this option logistically unfeasible. Twice-daily supervised methadone administration does have a role for a small minority. For the vast majority of heroin-dependent persons seeking help, methadone treatment achieves substantial benefits with few adverse effects.

Iodine deficiency

Editor, – I am an endocrine surgeon working with a diverse overseas-born population. I have been checking the iodine nutritional status of my goitre patients recently, as iodine deficiency may be more common in Australia than previously thought. Only two or three patients out of 54 tested with normal iodine levels on 24-hour urinary iodine testing. One notable exception was a patient with 45 times the normal daily excretion. On questioning, she had not had recent IV contrast media or amiodarone, but had consumed a herbal cough mixture. The contents of the medicine are unclear.

Iodine does not appear to be listed on the box. The dose of half to one tablespoon without reference to frequency or age concerns me. Prescribers (and patients) need to be aware that herbal remedies can be hazardous. Patients with pre-existing goitre can become thyrotoxic if exposed to even a modest supranormal iodine load. Those with thyroid cancer who are given iodine by well-meaning naturopaths may delay or reduce the effectiveness of radioactive iodine therapy.

Peter Campbell

Endocrine Surgeon

Liverpool, NSW

Bisphosphonates – clinical applications in osteoporosis

Editor, – At last some common sense seems to be finding its way into medical thinking. Professor John Marley assures us of what we have all known at the back of our minds: that efficacy is not the same as effectiveness (Aust Prescr 2000;23:114-5). We have heard so much about evidence-based medicine and Cochrane reviews that we have barely escaped the conclusion that evidence-based, statistically sanctified, Cochrane-metanalysed* medicine is the *only* proper kind for us to practise. In the real world we are not free, as trial-makers are, to exclude patients because of age or concurrently taken drugs or comorbidities, so we have to use a little of that ancient virtue intuition when grappling with many problems.

Another improvement is that we are being given absolute risks along with 'risk reduction ratios'. The latter, of course, are the selling ploys of the drug companies – they seem so persuasive! Without the corresponding absolute risks they are virtually meaningless, and no basis for clinical decisions. The derivative parameter 'number needed to treat' (NNT), admirably set out in the article on bisphosphonates (Aust Prescr 2000;23:133-6), is much more useful. However, there are grave ambiguities: is the NNT based on the number of people to whom the doctor says 'I intend to treat you with a daily dose of Bonehardna for five years', or the number who actually comply with the treatment regimen? And is it the lifetime NNT or does it apply to a time-span such as a year? These points need to be stated.

Lastly, I have struggled to find meaning in the sentence: 'Increases were 4.3% greater than placebo in the lumbar spine, 2.8% in the femoral neck ...' (p.134, col. 2). 4.3% of what? If the placebo produced 100 units of improvement, did the risedronate produce 104.3? This is what the words seem to mean (and again, in how much time?), but it is hardly a strong recommendation, since the placebo is likely to have produced a negative benefit. Or does it mean something else? If it does, why not say so?

Alasdair Livingston

Surgeon

Mitcham, SA

* I decline to use the horrible word 'meta-analysis'. The Greeks had no qualms about eliding two or more prefixes together, and if we borrow their language, nor should we.

Associate Professor Peter Ebeling, author of 'Bisphosphonates – clinical applications in osteoporosis', comments:

I would like to thank Dr Livingston for his comments on 'Bisphosphonates – clinical applications in osteoporosis'. I agree with Dr Livingston that the absolute risk of an outcome is more important than the relative risk reduction, particularly when considering an individual patient's treatment. The duration of treatment required to calculate the number needed to treat appears in the tables and is for five years' and three years' treatment with alendronate and risedronate, respectively, in women with postmenopausal osteoporosis and at least one baseline vertebral fracture. For osteoporotic women without vertebral fractures, the number needed to treat was calculated for only four years of treatment with alendronate – as the data for the risedronate hip fracture study[1] had not been published at the time of preparation of the manuscript.

Regarding the changes in bone density in the risedronate fracture study, the differences between the treatment and placebo groups represent changes from baseline at three years, expressed as a percentage. In the placebo group small significant increases or decreases in bone density from baseline were seen depending on the skeletal site measured. Thus, treatment with calcium 1000 mg per day +/– vitamin D in the placebo group for three years resulted in a 1.1% increase in spinal bone density, but did not prevent bone loss from femoral sites in postmenopausal women with osteoporosis.

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Stopping antidepressants

Editor, – The article 'Stopping antidepressants' (Aust Prescr 2001;24:13-5) brings together many practical discussion points for pharmacists to reinforce the medical practitioner's treatment. However, in listing the factors influencing the decision to stop treatment, a significant omission as a factor is the continuing presence or otherwise of the trigger(s) which contributed to the original depression.

John Williams

Pharmacist

Mosman, NSW

Professor Isaac Schweitzer and Kay Maguire, authors of 'Stopping antidepressants', comment:

Mr Williams raises the role of triggers in precipitating and perpetuating a depressive disorder. This area remains somewhat controversial and each individual case must be considered in its overall context. Judgement is often required which can be difficult and complex. Did the depressive illness itself result in the difficult psychosocial situation of the patient or did psychosocial factors play a role in bringing on the illness? These are central questions which must be considered.

Prevention of endocarditis

Editor, – As a dentist, I am particularly concerned with guidelines for the prevention of endocarditis. The new Antibiotic Guidelines[1] differ from previous editions by giving only one set of recommendations for patients with cardiac lesions, which predispose them to infective endocarditis. These include congenital or rheumatic heart disease, a previous episode of endocarditis, and the presence of prosthetic heart valves. In previous editions there were guidelines for low-risk patients (those suffering from congenital or rheumatic heart disease) and for high-risk patients (those with prosthetic heart valves or a previous episode of endocarditis).[2] The prophylaxis for low-risk patients was 3 g oral amoxycillin given one hour before dental treatment. For high-risk patients this was supplemented with gentamicin 2 mg/kg.

In the new edition the dose of amoxycillin is reduced to 2 g and there is no additional drug for high-risk patients. I am unhappy about the omission of the category of high-risk patients because I am aware of three cases where oral amoxycillin failed to prevent the occurrence of endocarditis. A recent British paper[3] continues to advocate a supplementary antibiotic for high-risk patients.

The editors of the Antibiotic Guidelines do not explain these changes. They state 'Consensus is currently changing and these recommendations are based upon current international practice'. It would seem that on the whole the guidelines of the American Heart Association[4] were followed. Would it not be more logical to base the new recommendations on an analysis of case histories? One way of approaching this difficult subject would be by analysing instances where previous recommendations for prevention had failed. Unfortunately there is no central body responsible for listing such failures. The last such study[5] was published in 1982. We can only ascertain whether the prophylactic measures suggested by various authorities are effective or not, if records are kept.

It is unfortunate that guidelines for the prevention of endocarditis differ from country to country. I agree with the suggestion that we should have uniform guidelines throughout the world.[6]

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Professor W. John Spicer, Chairman, and Dr David Looke, Member, Writing Group for Antibiotic Guidelines, comment:

We empathise with Dr Ehrmann's difficulties. These difficulties stem from one currently insuperable problem in writing guidelines for endocarditis prophylaxis; there are no accurate, quantitative data on:

- the risks of particular procedures
- the risks of particular cardiac lesions
- the results of particular antibiotic regimens.

The Antibiotic Guidelines have been evidence-based for over 20 years, but in endocarditis prophylaxis, the evidence is like the Dead Sea Scrolls. It is fragmentary, imperfect, capable of various interpretations, or (mainly) missing!

Another problem in countries like Australia is that it is difficult logically or medicolegally to differ from major overseas guidelines when there are no data to show whether the outcomes of a different Australian recommendation would be similar, better or worse.

To address Dr Ehrmann's specific difficulties:

1. There is no good evidence to continue the practice of low-risk/high-risk stratification.
2. Three grams of amoxycillin was recommended originally simply because of the availability of that formulation. Pharmacokinetic data show that 2 g is enough. Certainly, 3 g is too much for some patients to tolerate. Whether or not a second dose would prevent endocarditis not prevented by a single dose, is pure conjecture.
3. There is no good evidence that gentamicin is necessary or effective in prophylaxis (as distinct from treatment). We have therefore moved towards the American and British recommendations.

Dr Ehrmann's comments are welcome and constructive. In this area with so little hard evidence, opinion must be gathered, weighed and synthesised into coherent recommendations. Variation is acceptable if good reasons and particular circumstances exist. Compromise is inevitable, and disagreement predictable.

'Take as directed', whatever that means

Editor, – I refer to the article ' "Take as directed", whatever that means' (Aust Prescr 2000;23:103-4).

In South Australia 'that' means the prescription is invalid. Regulations under the Controlled Substances Act require that prescriptions be legible and include *specific* directions. In most instances the problem is resolved by reference to prescription records and discussion with the patient, to avoid forcing the patient to return to the doctor to have the prescription corrected.

Helen Hopkins' article omits mention of the positive contributions made by pharmacists in aiding compliance, mentioning only ' ... hesitating to communicate effectively with consumers about risks'. We may hesitate in some cases but we distribute the majority of Consumer Medicine Information and other printed and verbal information available from health professionals. Many pharmacists also print the indication on the label at the request of the patient, but this is often difficult when prescribers do not indicate that the tricyclic, for example, is for pain relief.

It would be interesting to know how many patients refuse to take medication after reading the Consumer Medicine Information – we suspect many – because the early information sheets often contained misleading information.

Finally, the term 'polypharmacy' is inappropriate because it is poly-prescribing that leads to the problems of multiple medication use, something today's pharmacists try to discourage.

Peter Bayly
Pharmacist
Wattle Park, SA

Book review

Australian Medicines Handbook Drug Choice Companion: Emergency and Primary Care

Adelaide: Australian Medicines Handbook; 2001. 176 pages.
Prices:
Drug Choice Companion $60
Drug Choice Companion + AMH Book $190
Drug Choice Companion + AMH Book + CD $212

(Reduced prices for students and members of the Royal Australian College of General Practitioners, the Pharmaceutical Society of Australia and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists)

Ann-Marie Crozier, Director, General Practice Casualty, Balmain Hospital, Sydney

This is an excellent book for the practical general practitioner who wants to quickly check prescribing of drugs for the emergency situation.

The handbook assumes a basic knowledge of diagnosis of emergencies and acute medicine. Each presentation, e.g. pneumonia, migraine, unstable angina, is covered by a single page which helps the reader rapidly access the information. Emergencies are listed in an index in the back of the book. The book uses a pragmatic style with the drug(s) to be prescribed written in bold at the top of the page (including adult and child doses). Dot points expand on the management of the presentation. A short list of references, with preference for Australian references, is to be found at the back. The handbook is 17 x 11 cm (smaller than a prescription pad) in size and therefore would fit easily in most general practitioners' emergency kits. Whilst the stated purpose of the book is for doctors working in regional and remote Australia, there is a wealth of concise and relevant information for urban practitioners.

A number of sources have contributed to the handbook including the Royal Australian College of General Practitioners, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, and the Pharmaceutical Society of Australia. I note with interest that virtually all the general practitioners who have had input are from rural Australia including places like Tumut, Minlaton, King Island, Katherine, Wiluna and Thursday Island. Specialists throughout Australia and across a range of specialities have also been consulted.

The content of the protocols is based on evidence from resources such as *Australian Prescriber, Therapeutic Guidelines*, NHMRC guidelines, the *Medical Journal of Australia*, the Cochrane databases and emergency medicine texts, with a preference for Australian data where possible. The protocols are grouped according to organ systems. Drug choices in each protocol are ranked according to evidence about their efficacy, cost, tolerability and dosing schedule convenience. The dot points at the bottom of each page include advice on non-drug treatments and in some instances when not to use particular drugs.

The book is perhaps limited by its medication focus and its size. Conditions such as bradycardia, acute iritis and pericarditis do not appear. Emergencies where a drug focus is not paramount, such as burns, pneumothorax, barotrauma and heat stroke are not covered. This limits the book's potential as a complete emergency text and whilst this is not its stated aim, perhaps a greater coverage of emergencies and acute medicine would ensure that it could become the definitive emergency text for general practitioners. The index could be slightly expanded. For example, neither 'fit' nor 'convulsion' is listed whilst 'febrile convulsion' and 'status epilepticus' are. Tetanus prophylaxis is neither indexed nor addressed and again this may be beyond the scope of the book. Having said this, these minor negatives should not detract from the overall assessment which is that of a useful, concise and relevant emergency drug handbook.

I believe this is definitely a valuable addition to the working general practitioner's essential texts for the management of emergencies and acute medicine.

Management of the acute coronary syndromes

Con Aroney, Director of Coronary Care, Prince Charles Hospital, Brisbane

SYNOPSIS

Patients with acute coronary syndromes may be divided into those who have had a myocardial infarction with ST elevation on their ECG, and those without ST elevation. The latter group can be further classified as having a high, intermediate or low risk of death or having a myocardial infarction. These risks are stratified by newly determined clinical and ECG criteria, and specific serum markers of myocardial injury. There are protocols for the evaluation of chest pain. Structured protocols are used to assess intermediate risk patients in order to reduce the incidence of 'missed infarcts' and to facilitate early discharge where appropriate. Patients have a high risk if they have pain at rest, ST depression and elevated serum troponin. They are actively managed with combined medical and invasive therapy. Low molecular weight heparin and IIb/IIIa platelet receptor blockers have become an important part of management.

Index words: myocardial infarction, unstable angina, fibrinolytic therapy.

(Aust Prescr 2001;24:56–8)

Introduction

The acute coronary syndromes include unstable angina[1] and myocardial infarction. In patients with myocardial infarction the ST segment may or may not be elevated. Some patients without ST elevation do not develop Q waves although their serum markers demonstrate they have had an infarct.

These ECG changes, when combined with new serum markers of myocardial damage, can help in the assessment of patients with chest pain. This assessment suggests which patients will benefit from new drug treatments and revascularisation.

Aetiology

The patient's presentation is partly determined by the degree and duration of the reduction in coronary blood flow, the quality of collateral flow to the jeopardised myocardium and the nature of the thrombus which forms after an atherosclerotic plaque has ruptured. Patients with unstable angina or an infarction without ST elevation usually develop a white (platelet) non-occlusive thrombus. Approximately 80% of myocardial infarctions with ST elevation are associated with a red (fibrin with entrapped erythrocytes) occlusive thrombus.

The differences in treatment reflect these differences in pathophysiology:

- low molecular weight heparins (LMWH) and platelet glycoprotein IIb/IIIa inhibitors are effective for patients who present without ST elevation
- fibrinolytic therapy is useful for patients who have an infarct with ST elevation.

New serum markers

Cardiac enzymes, such as creatine kinase (CK), are often measured in patients with chest pain. These tests may not be specific for myocardial injury.

Cardiac troponins

Unlike the MB isoform of creatine kinase (CK-MB), the cardiac troponins are specific markers of myocardial injury. The presence of cardiac troponin I or T in the serum confirms myocardial damage. The serum concentration of cardiac troponin correlates with the subsequent risk of cardiac death and myocardial infarction, and is superior to CK-MB in predicting adverse events. CK-MB is now becoming an obsolete non-specific marker. Diagnosis and risk stratification are better achieved with the use of cardiac troponin I or T along with total CK.

Cardiac troponin should be remeasured 6–8 hours after chest pain presentation to exclude myocardial injury. Patients with elevated cardiac troponin but normal CK (or CK-MB) are a recently identified high risk group with an adverse prognosis and have been classified as having 'minor myocardial damage'.

Cardiac troponins are also elevated with other forms of cardiac injury. They are increased by myocarditis, severe cardiac failure and severe pulmonary embolism with right ventricular strain, and in patients with severe renal failure who have occult coronary disease.

The cardiac troponins can be used to 'tailor therapy' as they predict response to treatment with:

- LMWH in acute coronary syndromes without ST elevation[2]
- tirofiban in acute coronary syndromes without ST elevation[3]
- adjunctive use of abciximab with percutaneous coronary intervention.[4]

Management of ST elevation myocardial infarction

Patients with symptoms of less than 12 hours duration and ECG changes of ST elevation or left bundle branch block require emergency reperfusion. They should be given aspirin,

glyceryl trinitrate (for treating associated vasospasm), morphine and supplemental oxygen. Arrhythmias, acute heart failure or shock need specific management. Emergency department protocols for emergency reperfusion, with either percutaneous coronary intervention (PCI*) or fibrinolytic therapy, depend on the available facilities and personnel.

If PCI is available and can be performed by an experienced operator within one hour of presentation, it is often considered the treatment of choice. Immediate PCI has long-term advantages over fibrinolytic therapy.[5,6] Adjunctive therapy with abciximab should be given with PCI unless contraindications are present.

Where PCI is unavailable, fibrinolytic therapy is indicated for all patients without contraindications. Alteplase is preferred to streptokinase as it provides superior coronary patency and clinical benefits and a lower incidence of adverse effects. Newer fibrinolytic drugs (reteplase, tenecteplase) are convenient as they can be given as a bolus.

The most important complication of fibrinolytic therapy is bleeding, in particular intracranial haemorrhage. Uncontrolled hypertension (especially above 170/100) is a strong risk factor for intracranial haemorrhage. It is a contraindication for fibrinolytic drugs and should be controlled before fibrinolytic therapy. Patients with contraindications should be considered for immediate transfer to a unit equipped for PCI.

Management of patients without ST elevation

Compared to the management of patients who have a myocardial infarction with ST elevation, the management of patients with chest pain without ST elevation is less defined. It can be guided by risk stratification.

Risk stratification

The risk of the major cardiac events of death or myocardial infarction at six months is greater than 10% in high risk patients, 2–10% in intermediate risk patients and less than 2% in low risk patients.

High risk patients

These patients have any of the following:

- ongoing pain
- ST depression (greater than 0.5 mm) or deep T wave inversions in three or more leads
- elevated serum troponin
- recent (less than one year) history of infarction or revascularisation
- heart failure, shock or syncope.

Intermediate risk patients

These patients have:

- a history of prolonged, repetitive chest pain or pain at rest
- recent onset of angina (less than two weeks)
- a remote (greater than one year) history of infarction or revascularisation
- age over 65 years
- diabetes
- no high risk features.

Low risk patients

These patients have:

- a worsening anginal syndrome without prolonged, repetitive or resting chest discomfort
- normal ECG
- no detectable troponin
- no high or intermediate risk features.

(This group can be medically managed as outpatients, but should be referred for a cardiology assessment, preferably within two weeks.[1])

Rapid evaluation of intermediate risk patients

Patients who present with prolonged chest discomfort, but without new ECG changes or baseline elevation of serum troponin, are given aspirin. They are then recommended to undergo a rapid but intensive strategy of observation (for at least eight hours) and investigation. This includes cardiac monitoring, frequent ECGs (every three hours) or ST segment monitoring, repeat serum troponin at 6–8 hours, and, if patients remain pain-free with all tests negative, an exercise stress test before discharge.

Any positive results call for a reclassification into a high risk group and intensive treatment. LMWH is not recommended unless the patient is reclassified as high risk (for example, further pain, ECG changes or elevated troponin).

A rapid effective evaluation strategy for intermediate risk patients has the advantages of:

- reducing the incidence of 'missed infarcts'
- providing early identification (and treatment) of patients who develop high risk features during the observation period
- allowing prompt discharge of patients reclassified as low risk after the observation period.

Management of high risk patients

Patients with high risk features, but no ST elevation, are managed with aspirin and beta blockers. They are also given LMWH or intravenous tirofiban with unfractionated heparin. Patients with elevation of serum troponin have been shown to specifically benefit from treatment with LMWH or tirofiban.

A change from LMWH to tirofiban with unfractionated heparin is particularly indicated for patients with refractory ischaemia while on LMWH and for rural patients to facilitate their safe transfer to a tertiary hospital. Intravenous tirofiban should only be given along with unfractionated heparin (there is ongoing research to assess its administration with LMWH).

High risk patients benefit from a complementary aggressive medical and invasive strategy. Such a strategy[7] using initial

* Balloon angioplasty, often with coronary stent implantation

treatment with LMWH followed by early invasive therapy (with early angiography and PCI or bypass surgery) provides major benefits compared to an initial conservative strategy. There is a statistically significant reduction in:

- subsequent angina (22% vs. 39%)
- hospital readmission (31% vs. 49%)
- death or infarction (9.4% vs. 12.1%).

The benefit of PCI is enhanced by periprocedural treatment with IIb/IIIa blockers, particularly in patients with an elevated serum troponin.

Long-term management

Patients who have had a myocardial infarction or are in the high risk group should be referred to a cardiac rehabilitation program, with education, risk factor modification and regular exercise. Attending such a program leads to major improvements in functional health outcome, increased confidence, reduced depression and anxiety as well as a 20% reduction in death or infarction.

Long-term aspirin (or clopidogrel where aspirin is contraindicated) is recommended except possibly in patients with poorly-controlled hypertension. Beta blockers are indicated after myocardial infarction particularly in high risk patients with heart failure. ACE inhibitors are indicated, not only in patients with heart failure or left ventricular dysfunction but also in patients with other risk factors, especially diabetes and hypertension. In a large placebo-controlled study[8], patients with additional risk factors who were randomised to long-term ramipril had significant reductions in cardiac death, reinfarction and stroke. Long-term statin therapy is recommended after acute coronary syndromes if the patient's serum cholesterol is greater than 4 mmol/L.

Summary

Improved diagnosis and risk stratification of patients with acute coronary syndromes, using structured assessment protocols and specific serum markers (cardiac troponin), have led to the identification of those patients who benefit from aggressive medical and invasive treatments. This approach to management will provide a strong framework for future advances in therapy.

Dr Aroney is a member of the writing group for developing new guidelines for the management of unstable angina, for the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.

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Self–test questions

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

1. The MB isoenzyme of creatine kinase is the most specific marker of cardiac damage.
2. Patients who present with prolonged chest pain and ST elevation should be treated with a glycoprotein IIb/IIIa inhibitor if percutaneous coronary intervention is not available.

Prescribing curriculum for senior medical students

The National Prescribing Service (NPS) is working with the 11 medical schools in Australia to develop a prescribing curriculum for senior medical students. The departments of pharmacology have agreed to develop their own modules on prescribing, following identification of interns' specific needs.

There was consensus as to the type of curriculum needed. It should use self-directed learning and be:

- modular
- problem-based
- adaptable to groups
- web interactive.

The prescribing curriculum will recognise the environments in which interns work and the common conditions they face.

The curriculum is now undergoing technical testing and is expected to be finalised by the end of 2001.

Postgraduate medical councils are interested in extending the prescribing curriculum to first- and second-year postgraduate students, and are currently working with the NPS on this.

Treatment of vaginitis and vulvitis

Gayle Fischer, Dermatologist, Westmead, New South Wales

SYNOPSIS

The range of conditions that can cause vulvovaginitis is large and includes infective and non-infective causes. Although *Candida albicans* is a common infective cause, it is essential to consider other diagnoses. A diagnosis should be made from the clinical presentation, history, bacteriology and in some cases histopathology, before starting treatment. The treatment can then be based on the precise aetiology.

Index words: vulva, vagina, lichen sclerosus, candidiasis.

(Aust Prescr 2001;24:59–61)

Patient presentation

Women with vulvovaginitis may present with itch, discharge, dyspareunia, burning, soreness, dysuria and swelling. Symptoms may vary with the menstrual cycle. Symptoms are often not a reliable clue to diagnosis, and patients with a variety of different conditions may experience similar symptoms.

Which conditions cause vulvovaginal symptoms?

Although fungal infections are common they are not the only cause of vulvovaginitis (see Table page 63).

Infections

C. albicans can cause acute, recurrent and chronic symptoms that always involve the vagina and may also spread to the vulva.

Trichomonas can cause itching and an offensive discharge. Bacterial vaginosis causes a non-irritating discharge.

Group B and sometimes D streptococcus may occasionally cause a vaginitis with a persistent non-offensive discharge, which may cause maceration and irritation of the vulval skin. This infection may co-exist with *C. albicans*.

Herpes simplex does not cause a vulvovaginitis in the true sense. The patient presents with pain and discrete ulcers and blisters on the vulva.

Human papilloma virus causes genital warts. It does not cause itch or discharge.

Tinea is an uncommon cause of vulvitis, but does not cause vaginitis. A scaly rash with a well-defined edge that may extend onto the thighs is characteristic.

Non-infective conditions

When dealing with women with vulval symptoms remember that disabling pain and burning may occur in the presence of a completely normal vulva and normal bacteriology. These patients do not have vulvovaginitis and may prove to have neuropathic or referred pain.[1] Rarely is the complaint 'psychogenic'. Despite their lack of apparent abnormality the patient's symptoms should be taken seriously.

Dermatitis

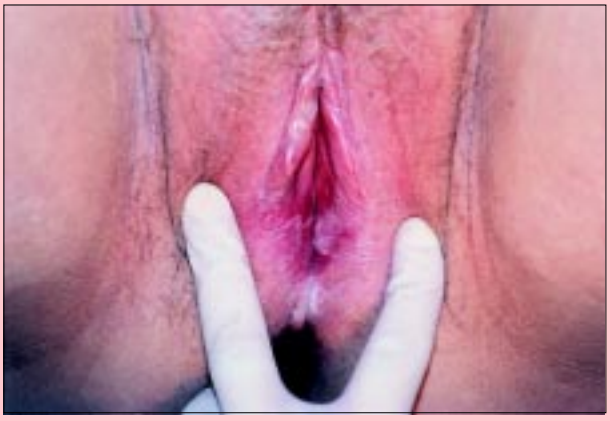
This is the commonest cause of vulvitis (see picture). It is most often found in atopic individuals, but they may not have a history of dermatitis on other parts of the body. Atopic dermatitis invariably has itch as part of the symptom complex. There is an observable erythematous scaly rash, with fissuring and desquamation involving the labia majora and minora. Atopic dermatitis does not involve the vagina.

Allergic or irritant vulvovaginitis is a dermatitis involving parts of the genital tract that have been exposed to irritating or allergenic substances. This includes imidazole antifungals, neomycin, latex condoms, perfumed oils, overuse of soap and bubble baths, and in rare cases seminal fluid. The dermatitis may be very severe and ulcerative, so that pain and burning are the main symptoms. Urinary and faecal incontinence may also cause a chronic irritant dermatitis.

Psoriasis

Approximately 2% of the population has psoriasis. In some individuals it may involve only the genital and perianal skin which can make it hard to diagnose. This itchy and sometimes sore condition does not involve the vagina. There is an erythematous, well-defined rash involving the labia, perianal skin and often the natal cleft.

Vulval dermatitis. The labia majora and minora are erythematous and scaly. There are areas of white discolouration due to lichenification that raise the possibility of vulval intraepithelial neoplasia as a differential diagnosis.



Picture provided by Dr Gayle Fischer

Lichen sclerosus

This is a relatively rare, but significant condition. It causes vulvitis only and does not involve the vagina. The very characteristic rash is a white plaque which may involve any part of the vulva or perianal skin. Often there is a telangiectatic or purpuric element. If untreated, shrinkage and scarring of the vulva with loss of the labia and clitoris and stenosis of the introitus may occur. There is a small but real association with carcinoma of the vulva.

Atrophic vaginitis

Patients who have low oestrogen levels due to menopause or lactation may develop vulvovaginal symptoms of varying severity. The commonest is vaginal dryness which inhibits sexual intercourse. Fragility of the epithelium may result in very small but painful fissures which make intercourse painful. In patients with an underlying atopic diathesis, vulval dermatitis may appear at times of oestrogen deficiency, and in addition to difficulties with sexual intercourse the patient may experience itching or a dermatitic rash. Examination reveals a pale, flat, dry mucosal surface often with tiny fissures around the introitus.

Diagnosis

As the treatment is based on the precise aetiology of the patient's condition, the first step is to make a correct diagnosis.

History

A comprehensive history is taken, particularly when symptoms are long-standing. Take the history of the presenting illness, an 'environmental history' (habits, possible allergens and irritants), dermatological history, gynaecological history, general medical and drug history and a psychosexual history.

Examination

Determine whether a rash is present and whether it is confined to the vulva or also involves the vagina. Occasionally dermatitis and chronic candidiasis may present with no abnormality (often due to recent treatment). However, close inspection may reveal subtle erythema, desquamation or fissuring that are signs of a skin condition. Both psoriasis and lichen sclerosus have characteristic appearances, and diagnosis can often be made on clinical examination.

Bacteriology

All patients need to have a vaginal swab to rule out *C. albicans* or other pathogens. The pathology lab should be asked to perform microscopy and to report organisms that would ordinarily not be considered to be pathogens. Recent use of antifungal medication will create a false negative, unless the treatment stopped a month before the swab was taken.

Where there is a suspicion of genital herpes, and blisters, erosions or ulcers are present, a viral swab should be taken from the lesion. When an offensive discharge is present a high vaginal swab should be taken.

When the vulva is involved a skin swab should be taken to check for bacterial infection. If tinea is suspected a skin scraping should be taken.

Histopathology

In some cases the cause of the rash may be elusive or it may be necessary to differentiate conditions that look similar. A biopsy should be taken where possible to confirm lichen sclerosus (because of its serious implications) and where malignancy is suspected.

Treatment

Dermatitis and psoriasis

Environmental modification is the first and most essential step, without which treatment is likely to fail. It is also essential to explain the concept of chronicity to these patients, to avoid disappointment if relapse occurs.

Irritating substances (soap, bubble bath, essential oils, antifungal creams, perfumed toilet paper, perfumed sprays) and occlusive clothing (tight jeans, pantyhose, G-strings, nylon underwear and sporting gear, pantyliners, pads) should be abandoned permanently. Cotton underwear, stockings, and tampons rather than pads should be used. A soap substitute is needed. A bland moisturiser that is tolerated by the patient without stinging (vaseline, aqueous cream) can be used daily to reduce dryness and fissuring.

All possible allergens should be eliminated. If there has been a very severe reaction to a suspected allergen, this can be confirmed by applying the substance to the forearm under a band-aid spot for 48 hours, or by formal allergy testing.

When dyspareunia is present, the woman may choose to abstain from sexual activity until she has recovered.

If skin swabs show a clinically relevant infection (most often *Staphylococcus aureus*), treat with an appropriate antibiotic.

Topical steroids are the treatment of choice for dermatitis and psoriasis. Treatment starts with a potent topical steroid such as methylprednisolone aceponate or betamethasone valerate ointment until the woman is symptom free. Patients must then switch to 1% hydrocortisone for another month before ceasing treatment. Environmental measures should stay in place indefinitely. Relapses are treated immediately with 1% hydrocortisone if mild, or a more potent ointment if severe. The patient is instructed to return for review and not to continue to self-medicate if there is no response in a week.

Certain topical steroids (mometasone, aclometasone) are very likely to cause severe stinging on the vulva. They should be avoided.

When using topical steroids on the vulva, remember that long-term use of a potent preparation may eventually cause cutaneous atrophy, striae, and secondary candidiasis. However, usage for a few weeks at a time is safe and is often necessary to induce a remission.

When treating psoriasis, initial management is the same as for dermatitis, but maintenance therapy with 1% hydrocortisone alone may not be possible. Addition of a tar-containing preparation is the best choice (for example, 2–4% liquor picis carbonis in aqueous cream).

Lichen sclerosus

The treatment of choice for this condition is a superpotent topical steroid such as betamethasone valerate in an optimised vehicle. This is used twice daily for one to two months, then daily until the patient is symptom free, and the white skin changes have reversed. If scarring or fusion is present this will not recover, and it is common to see post-inflammatory hyperpigmentation. Warn the patient that the ointment may sting at first but to persevere as there is no alternative.

Once the patient has improved, maintenance therapy is needed indefinitely. Most patients will require regular daily to weekly use of a moderately potent topical steroid. All patients need to be monitored every six months indefinitely for evidence of squamous cell carcinoma and for the adverse effects of topical steriods.

Atrophic vaginitis

Treatment of atrophic vaginitis involves the use of topical oestrogen if vulvitis is the only problem. If the patient is experiencing systemic symptoms, hormone replacement therapy is required. Oestrogen creams or pessaries are initially used daily for two weeks then once or twice a week depending on response. There should be an improvement within a month, and if not an alternative diagnosis should be considered. Where there is a concurrent dermatitis, 1% hydrocortisone ointment should be used daily with a lubricating emollient and a soap substitute. Stronger topical corticosteroids will worsen the atrophy and should be avoided. An oestrogen pessary will be preferable as cream may cause burning where dermatitis is present.

There is no place for the use of oestrogen cream in any condition other than atrophic vulvovaginitis. When used in other situations, oestrogen cream serves only to cause vulval irritation.

Chronic vulvovaginal candidiasis

This situation is very different from an attack of acute candidiasis, and will not respond to a single course of topical antifungal therapy. These patients have a real problem with eradication of this organism from the vagina. Although in most cases their immunity is quite normal, diabetes and iron deficiency anaemia should be ruled out.

Chronic candidiasis may be a difficult condition to diagnose, as 15% of women carry Candida in the vagina. Most of these carriers however will be asymptomatic. The combination of chronic vulval symptoms (especially when there is a premenstrual exacerbation or an exacerbation with oral antibiotics) and repeated positive vaginal swabs, is very suggestive of the condition. Examination usually reveals a very inflamed introitus and vagina, with a rash that may spread to the labia. However, sometimes there is very little to see.

When chronic candidiasis is suspected, a trial of therapy with an oral antifungal can be commenced. Although this has not been well researched it is often efficacious and avoids the use of possibly irritating topical antifungals. The only problem is cost, but the results usually justify it. Oral itraconazole, fluconazole or ketoconazole may be used. (The latter is less favoured because of the risk of drug-induced hepatitis.) The medication should be used daily until the symptoms have remitted (anything up to six months) and then weekly for another three months. The addition of 1% hydrocortisone ointment will help with itch in the early stages.

Many patients find that when they stop therapy relapse occurs. At present we have no answer for this situation other than continued intermittent dosing with oral antifungal medication (weekly to monthly as tolerated).

Summary

- Always use the history, examination and bacteriological investigation to make a precise diagnosis before treating vulvovaginitis.
- Never assume a patient with vulval symptoms has 'thrush' unless there is a characteristic history supported by positive microbiology.
- Always consider the possibility of a non-infective corticosteroid responsive skin disease, particularly when there is no vaginal involvement.
- Long-term environmental modification is needed when treating vulvovaginal disease.
- Use of potent corticosteroids on the vulva may be a necessary part of treating vulvovaginitis. They may be safely used for limited periods.

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Self-test questions

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

3. Atopic dermatitis is a common cause of vaginitis.
4. Diabetes should be excluded in women chronically infected with *Candida albicans*.

The treatment of *Candida* vaginitis and vulvitis

Graeme Dennerstein, Senior Associate, Department of Obstetrics and Gynaecology, Mercy Hospital for Women, Melbourne

SYNOPSIS

Vulvovaginitis may have an infectious cause, a non-infectious cause or a combination of both. A vaginal swab is usually needed to establish the diagnosis even though *Candida albicans* is the commonest infectious cause. Treatment of vulvovaginitis may require modification of the vaginal environment. Specific treatment for *C. albicans* involves inserting an antifungal drug into the vagina when the patient is symptomatic. Patients with recurring infections may need long-term prophylaxis with an oral antifungal drug. The diagnosis must be reviewed if patients do not respond to treatment.

Index words: candidiasis, antifungal drugs.

(Aust Prescr 2001;24:62–4)

Introduction

Candida albicans is the commonest cause of vulvitis and vaginitis. However, it is not the only cause and the clinician must be aware of the common conditions which produce similar symptoms (Table 1). Vaginal swabs and vulval biopsy are the most useful tools for differentiating these conditions.

Myths, traps and sexual sequelae

Candida reaches the vagina via oral ingestion. It is not sexually transmitted. It is therefore unnecessary to recommend treatment of the male partner unless he has candidal balanitis or another form of cutaneous candidiasis in the genital area.

C. albicans infection is an oestrogen dependent disorder. It therefore seldom occurs in healthy children, women who are breastfeeding or postmenopausal women unless they are on relatively high doses of oestrogen replacement. The infection almost always occurs within the insensitive vaginal lumen. The resultant 'burning' of the sensitive vulval epithelium is caused by the yeast's metabolites (seldom by infection of the vulval skin). Treatment must be directed to the vaginal source of the infection. Applying antifungal preparations to the vulva will not only be ineffective but will also worsen the contact dermatitis which is a feature of the complaint.

Mixed pathology is common in the vulval area. The commonest combination is vulval dermatitis exacerbated by bouts of candidiasis. Swabbing as often as necessary is the only means of selecting the appropriate treatment. The inappropriate use of antifungal applications can make the dermatitis worse as these products are relatively toxic to genital epithelium.

Candida species other than albicans are being diagnosed with increasing frequency. Examples are *Candida glabrata*, *krusei*, *parapsilosis* and *tropicalis*. These non-albicans yeasts are relatively non-pathogenic and rarely, if ever, require treatment. This is fortunate, because they are generally resistant to the usual antifungal drugs, and the over-the-counter availability of these treatments is probably why these yeasts are being selected out and appearing more often. This is also why pathologists must identify the species in all cultures positive for Candida.

Any woman who has genital discomfort for longer than, say, six months may develop impairment of sexual arousal. Dyspareunia can result from a combination of coital physical, chemical and biological trauma.

Recurrent candidiasis is an undoubted problem and the vast majority of sufferers are healthy women. I am unaware of any dietary regimen, so-called 'natural products' or lifestyle modification (other than prolongation of breastfeeding) which makes any significant difference to the incidence of this complaint. The vast majority of these patients will not be diabetic. Glucose tolerance testing is indicated in the more difficult cases and always in the postmenopausal woman with *C. albicans* infection if she is not receiving hormone replacement therapy.

General principles of treatment

Health professionals

The importance of having a vaginal swab taken before starting any treatment needs to be particularly emphasised to the patient. If the patient does not respond as you would expect to your first treatment, stop everything and think again. Is your diagnosis correct? There is no place for the empirical use of vaginal antifungals if the patient does not get a complete and prolonged response to a one week course.

Patients' personal care

Inflamed epithelium is hypersensitive to chemical and physical trauma, therefore special care needs to be taken and only normal saline can be guaranteed safe for washing. Most patients will benefit from avoiding soap and other cleansing agents and bathing the area with normal saline (salt, two teaspoons to the litre) applied with cotton wool and gently patted dry with a soft towel. For the same reason, patients should be advised not to use home remedies, over-the-counter preparations and non-prescribed medication. In the sexually active, the avoidance of artificial lubricants should be discussed.

Table 1
Vulvovaginal inflammatory conditions

More common infections	*Non-infectious conditions*
Fungal Candidiasis Tinea cruris or versicolor Viral Herpes simplex Bacterial Gram positive cocci *Staphylococcus aureus* Folliculitis Furuncles Abscess Streptococci Erysipelas Gram negative cocci Gonococcal vulvovaginitis Gram negative bacilli Donovanosis Chancroid Spirochaetes Syphilis Mixed and non-specific Bartholinitis Parasites Trichomoniasis Pediculosis pubis Scabies	Spongiotic disorders (characterised by intraepidermal oedema) Irritant contact dermatitis Allergic contact dermatitis Atopic dermatitis (eczema) Psoriasiform disorders Psoriasis Lichen simplex chronicus Lichenoid reactions (epidermal basal layer damage) Lichen sclerosus Erosive lichen planus Erosive vaginitis Plasma cell vulvitis Lupus erythematosus Drug eruption Vesicobullous disorders Including pemphigus, erythema multiforme, pemphigoid, herpes gestationalis and dermatitis herpetiformis Granulomatous disorders Including Crohn's disease and sarcoidosis Vasculopathic disorders Including Behcet's disease and urticaria

Note: Bacterial vaginosis (Gardnerella infection) does not produce vaginitis.
Streptococci and coliforms are not vaginal pathogens

Treatment of *C. albicans* infection

Many preparations are effective in the treatment of candidiasis. A vaginal imidazole, inserted nightly for one week, is recommended as the standard treatment for candidal vulvovaginitis.

Treatment of recurrent candidiasis

There is no generally agreed definition of recurrent candidiasis. However, the infection may be deemed recurrent if there is a proven recurrence less than six months after a similar episode has been successfully treated. Unless further measures are undertaken, experience suggests that recurrences, at an unacceptable frequency, are likely.

Laboratory confirmation of each suspected infection is an integral part of the management. The woman should be advised to have a vaginal swab taken whenever she suspects a recurrence.

There are several strategies for the prevention of recurrent infection. One week of a vaginal imidazole is still the treatment of choice when clinical (proven) infection occurs.

Alteration of the vaginal environment

This may be accomplished by a change of contraception to depot medroxyprogesterone acetate (which provides oestrogen-free ovulation suppression). For women taking hormone replacement therapy a lower dose of oestrogen can be used.

Long-term vaginal therapy

The nightly insertion of one million units of nystatin in a vaginal cream, tablet or pessary (including during menstruation) can virtually be guaranteed to keep a woman free of candidiasis without producing any significant discharge during the day. This therapy should continue for six months in the more troublesome cases. It is the treatment of choice for pregnant women who have had more than one proven infection during the pregnancy. This prophylaxis should not be stopped until the onset of labour.

Long-term oral therapy

Ketoconazole, fluconazole and itraconazole are effective oral anticandidal drugs available in Australia. They do not attain a concentration in vaginal secretions which is sufficient for them to be recommended as the sole treatment for clinical infection but they are definitely effective for prophylaxis. There is evidence that fluconazole is the most effective and least toxic but, at the usual dosage of 100 mg orally twice weekly (for prophylaxis), the patient will pay almost $40 a week.

Ketoconazole 200 mg orally daily is over 80% effective in preventing recurrences, but reports of hepatotoxicity and occasionally other adverse effects reduce its attractiveness. Sometimes recurrences will occur unless the dosage is raised to 200 mg twice daily. Ketoconazole requires an authority prescription if it is supplied by the Pharmaceutical Benefits Scheme. Six months continuous treatment is recommended.

Treat each recurrence thoroughly

Many women, given ready access to microbiological diagnosis and safe in the knowledge that they can get rapid treatment for each recurrence, will settle on just that – medication with each proven recurrence. In the event of multiple recurrences I would recommend 14 days continuous use (including during

menstruation) of a vaginal imidazole cream and a simultaneous course of ketoconazole 200 mg twice daily for five days. In many cases this regimen will reduce the frequency of recurrences.

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ACKNOWLEDGEMENTS

Doctors James Scurry and Rod Sinclair were largely responsible for the classification of vulval disorders from which Table 1 has been extracted. I wish to thank Dr Sam Sfameni for his suggestions in the preparation of this article.

Self-test questions

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

5. Not all species of Candida found in the vagina need treatment with antifungal drugs.
6. Genital candidiasis rarely occurs in healthy postmenopausal women unless they are taking hormone replacement therapy.

Your questions to the PBAC

I am writing to express my concern with respect to the February decision of the Pharmaceutical Benefits Advisory Committee (PBAC) to list bupropion. Even in my small town we have been inundated by requests for the drug, from smokers of all types. This has been spurred on by both word of mouth and continued media coverage. Making an assessment of the relevance of the drug to that particular person has been all but impossible, with people fearful that if they do not get in quick they will not get the bargain price. To be honest it has been almost like a firesale at the local department store, with the hysteria to match.

It has been impossible to get through to the Health Insurance Commission for more relevant and urgent authority prescriptions because the staff are busy processing requests for bupropion. I am deeply concerned at the cost to taxpayers of this PBAC-induced mayhem, and what benefit there will be to Australian consumers.

Discussions I have had with patients reveal poor compliance with the drug. No associated rehabilitation program was offered in conjunction with the release of this drug, and there are no local resources to provide one on a mass scale.

All in all, this has got to be the poorest effort at listing of a drug by the PBAC that I have ever seen, and has put most general practitioners in an awkward position of having to decide how to respond to mass hysteria and pressure.

Dr Ewen McPhee

General Practitioner

Emerald, Qld.

PBAC response

At its September 2000 meeting the PBAC recommended that bupropion be listed as an authority required pharmaceutical benefit for use within a comprehensive treatment program, as short-term adjunctive therapy for nicotine dependence with the goal of maintaining abstinence. The recommended listing provided for only one application per patient per year and prohibited the authorisation of increased maximum quantities or repeats.

In making its recommendations, the PBAC considers the effectiveness, cost-effectiveness and clinical place of a product compared to other products. Where there is no alternative as was the case for bupropion, the PBAC compares the product with standard medical care and considers the benefits the new product will provide compared to the cost of achieving those benefits. The PBAC also took into account the comparative performance of bupropion and nicotine replacement therapy.

The PBAC considered treatment with bupropion to be clinically and cost-effective where compared to standard therapy and nicotine replacement therapy. The PBAC is of the view that the large number of Australians currently seeking this therapy is an encouraging indication that many smokers want to stop smoking, and that listing this treatment on the Pharmaceutical Benefits Scheme is entirely appropriate. Furthermore, the Commonwealth Government has a role in promoting the cessation of smoking as this is a public health issue.

In relation to the comprehensive treatment program requirement of the authority listing for bupropion, this need not necessarily be a formal rehabilitation program, and in fact may be limited to counselling by the prescribing practitioner. The manufacturer of bupropion advises that a comprehensive motivational support program in smoking cessation, developed by the company, was in place when the medication was first released, as a private prescription, in November 2000. Patient enrolment in the program may be initiated by the prescribing doctor, a pharmacist or the patient in response to a package insert outlining the program and relevant contact details. Encouragement for patients to access the well established national *QUIT* program is also appropriate as a source of motivational support.

The Health Insurance Commission (HIC) appreciates the frustration prescribers may have felt as they experienced difficulties in getting through to obtain telephone authorities when calls unexpectedly nearly doubled when bupropion was listed on 1 February 2001. The HIC responded by re-allocating staff from other areas and in some states, additional staff were recruited to assist during the period of high demand, which has since eased significantly.

Correction

One of the letters published in 'Your questions to the PBAC' (Aust Prescr 2001;24:7) mentioned celecoxib as a general benefit on the Pharmaceutical Benefits Scheme (PBS). This is incorrect. Celecoxib is listed on the PBS as a restricted benefit for chronic arthropathies (including osteoarthritis) with an inflammatory component.

Late-life depression: what can be done?

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SYNOPSIS

Depression is commonly unrecognised in the elderly. There is also the problem of defining depression in old age. Severe depression will commonly need to be managed in hospital. Major depression is usually treated in the community setting. Minor depression can be as disabling as major depression. Management of minor depression includes dealing with precipitating factors, helping the patient adapt, and judicious use of medication. If drug treatment is needed the newer antidepressants may be better tolerated by the older person than tricyclic antidepressants.

Index words: antidepressants, cognitive behaviour therapy.

(Aust Prescr 2001;24:65–7)

Introduction

The presentation of depression in older age is often less obvious than it is in younger people. A majority of people in their seventies and older have at least one physical disability, and depressed elderly patients are likely to focus attention on physical symptoms when they visit their general practitioners. Depression can easily be overlooked.

Recognition of late-life depression

The cardinal features of depression are lowered mood and loss of interest. However, older people are less likely than younger patients to acknowledge feeling depressed. This is one of the reasons depression may be overlooked in older people. Patients may attribute their symptoms (lack of energy, inability to concentrate, irritability, poor sleep, weight loss and feeling slowed up) to their age, rather than a psychological cause. They may feel less comfortable than younger patients in talking to their doctors about such symptoms.

General practitioners often do not have a lot of time to give to each patient. Commonly there is a queue in the waiting room. Older patients may be anxious not to take more than their share of the doctor's time. Yet people with physical handicaps or disabling medical illnesses are six times more likely than others of their age to have depressive disorders.

Another reason why some studies report that doctors often fail to recognise depression is that experts differ in what they understand by the term 'depression'. Disagreements relate mainly to the non-typical, less obvious, less severe cases, especially those where there is comorbidity with physical disorders, and when anxiety and certain personality traits obscure the presentation. This confusion may be shared by some general practitioners. They are good at recognising 'severe' cases, but are less inclined to record depression in non-melancholic cases, including what used to be called 'neurotic' or 'reactive' depressions.

Epidemiologists have tended to include only cases of major depression (with or without melancholia) and dysthymia when estimating prevalence rates of depression. They say that depression is much less common in older age. However, patients with minor depression (a shorthand term for those with significant depressive symptoms but without fulfilling all DSM-IV[1] criteria for the diagnoses of major depression or dysthymia) may be just as distressed and functionally disabled by their symptoms as those with major depression.

Minor depression is common in older age, with a steep increase in prevalence in people over 80 years of age. This rise is largely attributable to the age-related increase in physical morbidity. Functional decline and symptoms of medical illness may be depressing. In a recent American study of patients over 60 years of age presenting for primary care services, 6.5% had major depression and 15.1% had minor or subsyndromal depression.[2]

Depression itself can lead to a decline in functional ability and well-being as severe as that caused by chronic medical conditions. If this distress can be relieved and the patient's function improved, it is well worth identifying cases of minor depression.

Doctors therefore need to think to themselves, whenever an older patient comes to see them, 'Could this person be depressed?' This particularly needs to be considered in relation to conditions known to have a high correlation with depressive illness, e.g. dementia. If unsure, then explore this possibility with the patient.

Dementia

Depression and dementia may both present with psychomotor slowing, poor concentration, impaired memory, apathy, fatigue and sleep disturbance. In the absence of tearfulness or depressed mood, comorbid depression may escape notice. A trial of antidepressants may lead to remarkable improvement in mood, although in most cases of dementia there is progressive worsening of the cognitive impairment even if the depression does not recur.

Frontal lobe changes can lead to an apathy syndrome which may be mistaken for a depressive illness, and is unresponsive to antidepressant therapies. Other brain changes may lead to emotional lability, with pathological crying. A trial of antidepressants is worthwhile even in obviously organic mood syndromes.

Factors related to late-life depression

The first step in effective management of late-life depression is proper assessment. This includes a review of all factors that might be related to the development, persistence or lessening of depressive symptoms. Nature, nurture and life circumstances (including physical changes) may all have relevance when considering the aetiology of depressive disorders. There is a continuum between types of depression which are thought of as primarily biological and primarily psychological in origin, but there may be a secondary organic response overlapping both biological and psychological parts of the continuum. Particular consideration needs to be given to these organic factors when planning interventions for depressed older people.

Personality factors may affect whether someone will respond to certain events or situations by becoming depressed. Personality is partly determined by inherited characteristics and partly by upbringing. The meaning of events or situations to individuals (for example threats or insults) may well be determined by their experience of similar events earlier in life. Some may learn to react by being helpless and submissive, whereas others may learn assertiveness and acquire a need to be in control.

Losses may induce feelings of helplessness or anger. Bereavement may lead to prolonged sadness. Other losses (for example of accommodation, financial security, social network, independence, mobility, source of self-esteem) may also lead to persistent and comparable sorrow, loss of pleasure in life, a sense of emptiness, dwelling on the past, apathy about the future, and maybe frustration, anger and irritability. Loss of health may provoke feelings of insecurity as well as of wretchedness.

Ill health may precipitate depression through physical as well as psychological effects. Endocrine disorders such as hypothyroidism are obvious examples. Other causes include neoplastic disorders, vitamin deficiency and a host of neurological conditions such as stroke, Alzheimer's disease, vascular dementia and Parkinson's disease. Pain has a strong association with depression, but whether this is entirely through psychological processes is debatable.

Stress and emotional reactions provoke neurobiochemical changes, including release of corticosteroids. Thus psychological depressions have biological elements. Stress can lead to atrophy of stress-vulnerable hippocampal neurons by decreasing the availability of protective neurotrophic factors. This may explain why having one depressive episode makes it more likely that a person will have depressive episodes in the future. It may also explain why affective disorders which are believed to be mainly biological in origin (melancholia, bipolar and psychotic depression) are commonly precipitated by psychologically stressful situations.

There is also evidence that late-life depressions may occur in association with age-related (probably vascular) brain changes, in people who have not been diagnosed with dementia or other brain disease.

Management of late-life depression

If the clinical assessment reveals an obvious and reversible cause of the depression it should be reversed. Relevant physical disorders should be identified and treated. Situations or drugs which are contributing to the depression should be changed if feasible.

As part of the initial examination, the doctor should assess whether the patient is suicidal. If so, or if the patient has severe or psychotic depression, referral to specialist services is advisable and electroconvulsive therapy may be considered. In less urgent cases, inpatient assessment may well be appropriate and an adequate dosage of an antidepressant should be given. In cases of delusional depression a neuroleptic may be added (for example risperidone, olanzapine or quetiapine) although these are only approved on the Pharmaceutical Benefits Scheme for schizophrenia. The newer antidepressants are less likely than tricyclic antidepressants to cause distressing adverse effects and are less toxic in overdose; doctors usually prescribe selective serotonin reuptake inhibitors in therapeutic doses (usually one tablet daily) in contrast to the way tricyclic antidepressants and mianserin are used. However, venlafaxine and tricyclic antidepressants are commonly believed to be more effective in severe and resistant cases. It is always important to be aware of potential drug interactions. For example, moclobemide is preferable to selective serotonin reuptake inhibitors if the patient is taking warfarin.

When patients with severe depression fail to respond to adequate doses of antidepressants, electroconvulsive therapy is the best choice if the patient is willing. Some patients respond to lithium augmentation of antidepressants but it can be very difficult to manage in the elderly and the dose (titrated according to serum levels) is usually less than for younger people.

After recovery, patients who have experienced more than one episode of delusional or melancholic depression should stay on antidepressants (or a mood stabiliser if they have a bipolar disorder) for years. Even after just one episode, antidepressants should be continued for at least a year.

There is evidence that antidepressants can be effective in depressions associated with physical illness.[3] Experts suggest that the more severe depressions, even if precipitated by loss or stress, may respond to antidepressants, but there is only limited evidence for their effectiveness in milder depression.

In all cases of depression, psychotherapeutic support is appropriate. All patients should be enabled to ventilate their feelings and to discuss ways of adapting to their loss or distress. In cases of severe depression this may not be possible until they start to improve.

When depressions are loss-related (including bereavement, demoralisation and those associated with loss of health and functional capacity), the main focus of management will usually be psychosocial. Grief-work, cognitive behaviour therapy, interpersonal therapy, group therapy or counselling may be indicated. Stress and sorrow may be long-lasting, even though initial emotional responses may be regarded as adjustment disorders. Much depends on personality and

whether patients can adapt and move beyond their depressive reactions. Vulnerability and insecurity, which may become more pronounced in some people as they age, interfere with adaptation. This may be especially difficult for elderly migrants.

Symptomatic medication (e.g. hypnotics) may be useful for short periods, but prolonged use of anxiolytics is to be avoided. Antidepressants are preferable, and for many patients with persistent depression a combination of psychotherapeutic and pharmacological treatment is appropriate. Given adequate resources, a whole package of interventions aimed at enhancing physical and emotional well-being is desirable. If the doctor lacks skill to provide the appropriate psychotherapy component, a 'shared care' approach (linking with other health professionals) is recommended in these non-melancholic cases.

Prognosis

Most depressions in old age will respond to treatment, with consequent improvement in function and well-being, improved recovery rate from medical conditions, and reduced mortality rate. The prognosis for patients with severe depression associated with either dementia or deep white matter lesions is poor. Improvement may occur with treatment, but early relapse and treatment resistance are common. Comorbid physical disorders or severe anxiety may also lead to a protracted course.

Overall, the prognosis for late-life depression is no worse than for younger patients. Ageist and nihilistic attitudes to intervention should be abandoned.[4] Patients may take longer to respond, and treatment is often complicated, but there is good reason to be positive. Good liaison between general practitioners and psychiatry services for older people helps promote identification and appropriate treatment of late-life depression. Unfortunately, funding in Australia for such collaborative approaches is limited.

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Self-test questions

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

7. The prognosis for uncomplicated depression in old age is worse than for younger patients.
8. Selective serotonin reuptake inhibitors interact with warfarin.

Facilitators file

The National Prescribing Service (NPS) has provided funds to divisions of general practice to employ facilitators. These facilitators visit general practitioners to discuss common prescribing problems. During their visits the facilitators are finding some interesting issues. *Australian Prescriber* will publish some of these findings from time to time.

Thiazides and fractures

Some doctors are reluctant to prescribe thiazide diuretics. They fear that these drugs may put their patients at risk of having an osteoporotic fracture.

There has not been a randomised-controlled trial of the effect of thiazides on fractures. Some observational studies show a 60% increase in risk, while others show a 70% reduction in risk. To try to resolve the issue, researchers at the Garvan Institute in Sydney conducted a meta-analysis.[1]

The meta-analysis included 13 studies involving a total of 29 600 patients. It found that patients currently taking thiazides were less likely to have a hip fracture. The odds ratio (OR) was 0.82 with a confidence interval (CI) of 0.73–0.91. There was a trend for a reduction in all types of osteoporotic fracture (OR 0.88, CI 0.77–1.02).

While the odds of hip fracture were reduced with long-term use, short-term use of thiazides appeared to increase the fracture risk. This may be a result of patients having a fall when treatment begins.

Thiazides may influence the risk of fracture by decreasing the excretion of calcium. The authors of the meta-analysis suggest that thiazides should be considered as a method of preventing osteoporotic fractures particularly in patients with hypertension.

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Drug therapy of irritable bowel syndrome

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SYNOPSIS

Irritable bowel syndrome is a common disabling condition in the community. It is characterised by abdominal pain and disordered bowel habit, but the pathophysiology of the condition is unclear. Multiple factors including diet, gastrointestinal infection, disordered gut motility and emotional stress have all been implicated as potential triggers. Recent advances in our understanding of gastrointestinal physiology suggest that visceral hypersensitivity may underlie at least some of the clinical features. The key role of serotonin in gastrointestinal neural function has led to the development of new drugs that show therapeutic promise in management of irritable bowel syndrome. Treatment currently remains symptomatic with disorders of defaecation responding more readily than abdominal pain.

Index words: diarrhoea, hypersensitivity, spasmolytics, serotonin.

(Aust Prescr 2001;24:68–71)

Introduction

Irritable bowel syndrome is a group of chronic or recurrent gastrointestinal symptoms attributed to the small intestine and colon for which there is no underlying structural or biochemical explanation. The symptom complex is defined by abdominal pain and disordered defaecation. It may also be associated with features such as bloating and distension.[1] The diagnosis is based on identification of positive symptoms (Table 1) and the cost-effective exclusion of other clinical diagnoses with a similar presentation. In practice the diagnosis is often attached to any patient with an abdominal complaint where no other underlying pathology can be found.

Irritable bowel syndrome is common. It affects up to 15–20% of the population at any one time and is responsible for 30–40% of gastroenterology consultations. Many patients can be managed with advice on diet and lifestyle changes and do not require drug therapy. During the past 10 years better understanding of the pathways of gastrointestinal sensation have changed the strategy of drug development away from medications for abnormal gastrointestinal motility to drugs designed to modify visceral sensation.[2]

Aetiology

For many years irritable bowel syndrome was considered a psychosomatic condition with a heterogeneous presentation. Patient subgroups have been classified according to their dominant symptom combination, for example constipation- or diarrhoea-predominant. Although there has been a lot of research into the underlying causes there is no current unifying theory as to specific aetiology.

In an attempt to unify the various aetiological factors, a multifactorial model has been proposed in which inflammatory, allergic, dietary, genetic and psychological factors affect enteric visceral sensory neural pathways. These changes result in a hypersensitive system that overreacts to a wide array of emotional and peripheral stimuli.

Abnormal motility

Gastrointestinal smooth muscle has intrinsic patterns of motor activity which are under the control of the enteric nervous system. This is a complex network of nerves and ganglia located in the wall of the intestine. The motor activity is modulated by inputs from many areas via the autonomic nervous system and circulating humoral substances.

For many years gastrointestinal dysmotility was considered the main contributor to the symptoms of irritable bowel syndrome. Abdominal discomfort and pain were assumed to be caused by contractions that were too strong or prolonged, and disorders of transit were considered to result from altered patterns of gastrointestinal smooth muscle contraction. This approach provided a strategy for treatment. However, although there are a number of changes in gastrointestinal motor function,

Table 1

Rome II diagnostic criteria for irritable bowel syndrome*[1]

In the preceding 12 months, the patient has had at least 12 weeks (not necessarily consecutively) of abdominal discomfort or pain with two of the following three features:

- relieved by defaecation and/or
- onset associated with a change in stool frequency and/or
- onset associated with a change in form (appearance) of stool

Symptoms that cumulatively support the diagnosis of irritable bowel syndrome

- abnormal stool frequency (for research purposes may be defined as more than three bowel movements per day and less than three bowel movements per week)
- abnormal stool form (lumpy/hard or watery/mushy)
- abnormal stool passage (straining, urgency or feeling of incomplete evacuation)
- passage of mucus
- bloating or feeling of abdominal distension

* in absence of structural or metabolic abnormalities to explain symptoms

a clear relationship between symptoms and abnormal motility, in either the small intestine or colon, has never been shown. Irritable bowel syndrome is therefore probably not a primary motor disorder of the gut.

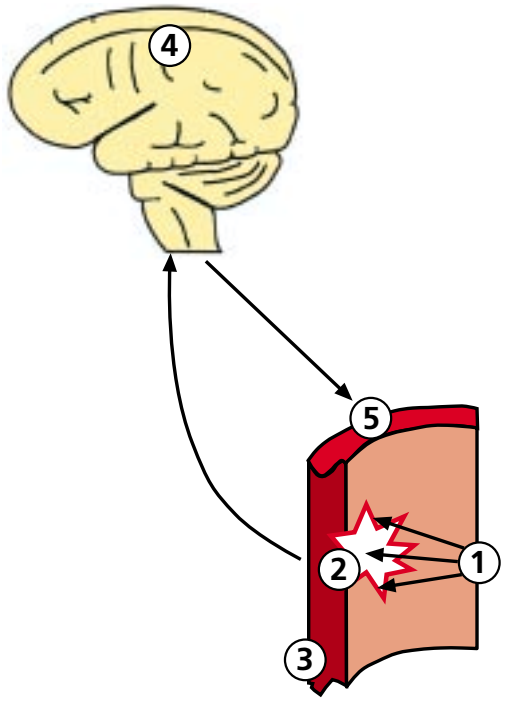
Abnormal sensation

Recent attention has focused on gastrointestinal sensation in patients with irritable bowel syndrome.[2] Stimuli within the gut (especially food) are continually sensed and sensory neural transmission integrated and processed by both the enteric nervous system and the central nervous system. Most of the sensory stimuli do not reach perception, but they can alter motor activity.

The key role of abdominal pain in irritable bowel syndrome led to the theory that abnormal gut sensation could underlie the condition with visceral hypersensitivity suggested as a possible aetiology. Irritable bowel syndrome patients are abnormally sensitive to distension throughout the entire length of the gut although their somatic sensitivity to painful stimuli is normal. Possible mechanisms that could result in abnormal visceral sensation are receptor hypersensitivity, abnormal integration or transmission of dorsal horn changes or changes in central processing perception (Fig. 1).

Fig. 1

Possible mechanisms for symptom production in irritable bowel syndrome



1. Abnormal stimulation of normal gastrointestinal receptors
2. Abnormal response of gastrointestinal receptors to normal stimuli
3. Abnormal gastrointestinal motility
4. Abnormal central perception of normal gastrointestinal afferent signals
5. Abnormal central stimulation of gastrointestinal tract via efferent pathways

(Courtesy Dr D. Armstrong, McMaster University, Canada)

Infection and inflammation

Many patients have a well-defined gastrointestinal infection preceding the development of irritable bowel syndrome. A number of investigators have described an increase in the mucosal mast cell population in post-infective irritable bowel syndrome. It is possible that these cells release inflammatory mediators which then affect enteric neurotransmitters and perpetuate symptoms associated with acute infection.

Role of stress

Acutely stressful situations are often associated with transient changes in bowel function. Their importance in irritable bowel syndrome is less clear, although they may function as triggers in some patients. Chronically stressful situations, particularly abuse in early life, have been associated with an increased incidence of irritable bowel syndrome.[3]

Non-drug treatment

Lack of exercise and insufficient time at stool are common problems which are relatively simple to remedy. Many patients also understand that anxiety can alter bowel function acutely and a positive diagnosis and explanation together with a supportive therapeutic relationship may be all that is required. In patients without major psychiatric disease, biofeedback and hypnotherapy have also been reported to be effective.

Specific dietary advice

Lactase deficiency is common, but its role in irritable bowel syndrome is uncertain and restriction of calcium intake especially in women needs monitoring because of the risks of osteoporosis. Many patients identify a dietary trigger for their symptoms and a sensible reduction in specific foods can be beneficial particularly for symptoms such as bloating and diarrhoea. Other patients eat large amounts of indigestible carbohydrate or artificial sweeteners and improve with appropriate restriction of these. In contrast, patients with constipation may require an increase in dietary fibre. Formal exclusion diets are time-consuming and require referral to a dietitian.

Drug treatment

In the absence of a well-defined aetiology, drug treatments for irritable bowel syndrome aim at the predominant symptoms.[4] As there is considerable inter- and intra-patient variability in the symptom pattern, it is perhaps not surprising that the response to many drugs is unclear. In addition, there is a 30–40% placebo effect which confounds drug efficacy studies.

Specific drug treatments for disturbed transit are the most successful treatments currently available for irritable bowel syndrome.[5] However, as patients' symptoms switch from constipation to diarrhoea, treatment strategies may also require modification.

Antidiarrhoeal drugs

Opiates have been used for centuries to reduce diarrhoea. These drugs slow gut transit largely by acting on specific sub-types (μ) of the opioid receptors of enteric nerves. The newer opioid drugs diphenoxylate and loperamide are preferred

to drugs such as codeine as they are relatively safe, effective and, as they do not cross the blood-brain barrier, they have minimal central effects. Loperamide may also increase anal sphincter tone. Patients can use these drugs as required and titrate the dose according to their needs, remembering that they may be quite sensitive to opiates and easily become constipated. Taking antidiarrhoeal drugs before travelling to work, social activities or stressful situations may enhance the patient's quality of life.

Drugs used to treat nausea, such as the 5-HT_3 antagonists granisetron and ondansetron, are well recognised causes of constipation. More recently alosetron, another 5-HT_3 antagonist, was shown to markedly slow left sided colonic transit, suggesting a possible future role for this class of drugs in diarrhoea-predominant irritable bowel syndrome. These 5-HT_3 antagonists may also affect gut sensation. However, alosetron has been withdrawn due to serious adverse effects.

Laxatives (Table 2)

The simplest means of tackling constipation is the addition of fibre (such as bran) to the diet. If bran is not tolerated other bulking agents such as psyllium can be substituted although these are more expensive. The goals of therapy need to be realistic and patients need to be warned of the potential adverse effects of bloating, abdominal distension and flatulence.

The addition of laxatives needs to be incremental and graded as it takes a few days to achieve a new 'steady state'. In addition to an increase in flatus production, they may exacerbate symptoms such as bloating and abdominal distension if the dose is increased too rapidly. Patients should be instructed to look for a bulkier, more easily passed stool as a sign that they are taking an effective dose of fibre. Bulking agents should be taken on both good days and bad days. If the predominant symptom switches from constipation to diarrhoea a reduction in bulking agents is indicated.

Drugs to reduce spasm

No drug has been convincingly shown to have benefits beyond placebo. Abdominal pain in irritable bowel syndrome has been treated with antispasmodic and anticholinergic drugs for more than half a century without them clearly being shown to be of benefit. Meta-analyses show some benefit over placebo for abdominal pain, but not for constipation.[6] Painful muscle cramps may be treated with drugs such as mebeverine, dicyclomine and cimetropium.

Muscarinic antagonists such as atropine or hyoscine that block cholinergic stimulation are non-specific smooth muscle relaxants. They may be helpful in reducing severe episodes of pain arising from gut spasm. These non-specific drugs may have adverse effects on the bladder, eyes and salivary glands. They are best used on demand rather than routinely.

Drugs to modulate sensory feedback

Tricyclic antidepressants

Up to half of the patients with irritable bowel syndrome show some clinical features of depression and these patients require appropriate treatment. There are however many observations which show that patients who are not depressed may benefit from taking tricyclic antidepressants in doses which are smaller than those used to treat depression (e.g. amitriptyline 10–50 mg). Although central modification of pain pathways may occur, the exact mechanisms of action are unclear as the tricyclic antidepressants also have anticholinergic effects.

Table 2
Drug therapy for constipation

Drug	*Dose*
Psyllium	1 tablespoon twice daily with meals
Methylcellulose	1 tablespoon twice daily with meals
Lactulose*	15–30 mL twice daily
Sorbitol*	20 mL 2–3 times per day

Suggested starting doses for bulking agents in treatment of constipation. Subsequent doses should be titrated against clinical effects.
* may cause bloating

5-hydroxytryptamine (5-HT) antagonists

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) has a key role in gastrointestinal motor function through its actions on nerve receptors within the enteric nervous system.[7] A number of receptor sub-types may be involved in gastrointestinal sensation. Most recently it has been suggested that 5-HT_3 receptors may have a key role in visceral hyperalgesia. Studies are ongoing with a number of 5-HT_3 antagonists to determine their effects on visceral hypersensitivity. Preliminary studies indicate that these drugs may improve symptoms such as urgency and abdominal pain in diarrhoea-predominant irritable bowel syndrome. It is unclear whether this effect is mainly due to the drug's action on gastrointestinal transit. A number of other drugs that modulate sensory transmission and perception are also under investigation.

Conclusion

There is at present no 'magic bullet' for the treatment of irritable bowel syndrome. This is not surprising in view of the variability of symptoms and the probability that multiple aetiologies contribute to symptoms. Many patients cope well with reassurance alone after exclusion of serious pathology. Drug treatment aims at symptom relief and is directed at maintaining normal work and recreational activities. Therapy needs to be individually tailored to the patient's current symptoms with a preparedness to switch strategies if the predominant symptoms alter.

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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]

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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 trial[1] had hormone-receptor positive tumours, the efficacy of exemestane in oestrogen-receptor negative tumours is uncertain.

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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 $5HT_2$ and $5HT_3$ receptors, the serotonin acts at $5HT_1$ 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.

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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.

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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.

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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)

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

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PRODUCTION

Production Co-ordinator
Reid, S.

Desktopping
Barnes Desktopping and Design

Australian Prescriber is indexed by the Iowa Drug Information Service, the Australasian Medical Index and EMBASE/Excerpta Medica.

Address correspondence to:
The Editor
Australian Prescriber
PO Box 100
Woden ACT 2606
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Printed in Australia by
National Capital Printing
22 Pirie Street, Fyshwick, ACT 2609

Published by the Commonwealth
Department of Health and Aged Care