Australian Prescriber

CELEBRATING 30 YEARS

VOLUME 28 | NUMBER 3 | AN INDEPENDENT REVIEW | JUNE 2005

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Editorial

Prescribers and drug withdrawals

Gillian Shenfield, Clinical Professor in Clinical Pharmacology, Department of Clinical Pharmacology, Royal North Shore Hospital, Sydney

Key words: COX inhibitors, drug industry, drug regulation.

(Aust Prescr 2005;28:54–5)

> 'Disingenuous surrogate markers and misleading composite outcomes may create good advertising material, but can obscure data and hinder genuine patient-centred care.'[1]

The much publicised withdrawal of rofecoxib and the subsequent queries about the safety of celecoxib evoked a huge response in both the lay and the medical press. Medical journals have thundered about the irresponsibility of the pharmaceutical industry and the lack of vigilance of government agencies.[2] These criticisms are generally justified, but the use of new drugs is not solely determined by industry and government.

Australia has a National Medicines Policy which is a partnership between health professionals, consumers, the government and the pharmaceutical industry. The Quality Use of Medicines (QUM) arm of the policy builds on this with advice on giving the appropriate drug, to the right patient, at the right time, by the safe and judicious use of high quality medications. Prescribers are central to this process and we must therefore bear some of the responsibility when things go wrong. We certainly share the brunt of the aftermath, as drug withdrawals create widespread panic and far more work than writing a prescription for a new drug. Could we have prevented the debacle with the cyclo-oxygenase-2 (COX-2) inhibitors before the recent trials made the importance of vascular adverse effects completely clear?

In this issue…

New drugs may be associated with new risks of harm. While Gillian Shenfield comments on the 'debacle with the cyclo-oxygenase-2 inhibitors', Daniel Worthley and Robert Fraser remind us that non-steroidal anti-inflammatory drugs are commonly associated with gastrointestinal bleeding.

New indications may also expose new risks. Gerard Byrne tells us that antipsychotic drugs may have cardiovascular adverse effects in patients with dementia.

While the risks of isotretinoin are now well-known, John Sullivan stresses the importance of ensuring patients know about the adverse effects and how to minimise them. Most smokers know about the harmful effects of tobacco, but are unable to quit. John Litt advises on new approaches to help them successfully stop.

Consider what happened in Australia. Celecoxib was first available on prescription in 1999 and numerous sample packs were given to both general practitioners and specialists. It was listed on the Pharmaceutical Benefits Scheme (PBS) in 2000 and in its first year it cost the PBS $200 000 000. This equalled the cost of **all** cytotoxic drugs in the same period. Why did this enthusiastic prescribing occur? Both celecoxib and rofecoxib were marketed as 'safer', rather than more efficacious, but the limited extent of the benefit was not made clear to prescribers.

In 1999 it was known that the major demonstrated effect of COX-2s, compared with non-steroidal anti-inflammatory drugs (NSAIDs), was a reduction in shallow 'endoscopic' ulcers which are clinically unimportant.[3] The beneficial effect on serious, complicated ulcers was very much less. In patients with rheumatoid arthritis and no other risk factors, the annual risk of developing a complication related to NSAID use is only 0.4%. COX-2s could possibly reduce this to 0.2% (likely to be expressed as a 50% reduction for marketing purposes). In this group it would be necessary to treat 500 patients to prevent one complicated ulcer. In younger, healthier individuals the 'number needed to treat' would be even higher.[3] Yet in Australia more than 50% of the patients prescribed COX-2s were under 65.[4]

Many doctors gained the false impression that selective drugs were also less likely than conventional NSAIDs to have adverse effects on blood pressure and the kidneys. This view was also held by some key opinion leaders – people who always have a major influence on prescribing patterns and, for this reason, are invited by pharmaceutical companies to talk to groups of prescribers. To complicate the situation, the media persuaded consumers that the new 'wonder' drugs were more efficacious than older medications. Word of mouth completed a marketer's dream situation. Certainly the drugs were heavily promoted by both industry and the media, but why did prescribers fail to follow QUM principles? The facts were all there[3] and there are many independent sources of information about drugs (see box).

Unfortunately, independent sources do not have the same resources as pharmaceutical companies and their information usually lags behind marketing campaigns. Independent organisations, such as the National Prescribing Service, are often perceived to be driven by cost containment when they advise cautious use of new drugs. In fact their caution usually relates to the paucity of safety data and limited experience with the drug.

Some sources of independent information

Australian Prescriber – www.australianprescriber.com

National Prescribing Service publications: Newsletter, RADAR – www.nps.org.au

Therapeutic Guidelines – www.tg.com.au

Australian Medicines Handbook – www.amh.net.au

There seems to be a glamour about anything new, despite the absence of long-term safety information when a drug is first approved. Of course the industry designs and interprets trials to maximise favourable outcomes. Of course it puts the best possible spin on its marketing messages, but doctors should be smart enough to see through the hype. They need to know that when a drug first appears on the market only limited safety data are available and long-term outcomes, both good and bad, can only emerge with time and appropriately designed, prospective safety studies. It is well established that most prescribers obtain the majority of their information from the pharmaceutical industry and they therefore need more training in how to evaluate the information and what questions to ask drug representatives.[5]

The National Prescribing Service in a recent publication suggests that we should think about what is not known rather than what is known about new drugs.[6] Medical schools and postgraduate colleges must take more responsibility for training students and young doctors about assessing new drugs. This involves more than just an extrapolation of evidence-based medicine. We cannot complacently offload all blame onto government regulators and industry.

Rofecoxib is by no means the first drug to be summarily removed from the market. Cerivastatin and mibefradil suffered a similar fate, in both cases because of fatal toxicity due to interactions with other drugs. There are also many examples of new drugs which have had significant safety warnings added to their product information within a few years of marketing.

There is no merit in being among the first to prescribe a new drug whatever the pressures from patients and drug companies. It has been well said that 'For all newly-licensed drugs, confidence about safety can only be provisional'.[1] It is essential that both prescribers and consumers grasp this fundamental fact.

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Further reading

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Professor Shenfield is on a number of National Prescribing Service committees, has chaired a writing group for Therapeutic Guidelines, and conducts reviews for the Australian Medicines Handbook.

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.

Expensive new drugs – do we really need them?

Editor, – Professor Moulds' editorial (Aust Prescr 2004;27:136–7) suggests that in the last 20 years, new prescription medicines have failed to provide the same therapeutic advances as in the previous 20 years, but are costing significantly more. Furthermore, Professor Moulds believes that patent protection for profiteering pharmaceutical manufacturers is denying the community access to cheaper generic medicines. I would like to dispute the professor on a number of issues.

First, data from the Australian Institute of Health and Welfare show that in the last 20 years, mortality rates have decreased for cardiovascular disease (48%), respiratory disease (33%), and digestive disorders (35%). Medicines have saved more lives in the last 20 years, however morbidity rates have inversely increased.

Secondly, it now costs over $1 billion for a pharmaceutical company to develop a single new medicine.[1] This is quadruple the cost of 20 years ago. If an innovator cannot recoup these development costs, they have less discretionary

resources to devote to the development of better and more efficacious medicines.

Finally, Australian patent law does not preclude a generic manufacturer from selling a copy of a drug with an expired patent, even if the innovator company advances the development in some way. Nor does Australian patent law allow innovators to make trivial patent applications. 'Evergreening' simply does not exist in Australia and never has.

There is a myth in Australia that generic medicines are cheaper. In reality, generics are cheaper for the government to purchase, but the cost savings have not been passed onto the Australian consumer. Ironically, the government increased the co-payment of Pharmaceutical Benefits Scheme (PBS) items in January 2005 by 21% to make headroom for new and expensive medicines on the PBS.

If we want more effective medicines, we should be encouraging innovation from manufacturers rather than accusing them of being greedy for wanting a return on their investment. The result is that patients who may benefit from a newer and more efficacious medicine will miss out.

Brendan Grabau
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Consultant pharmacologists
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Professor R.F.W. Moulds, author of the editorial, comments:

The main point of my editorial was that new drugs introduced over the last 20 (or so) years have not had the same impact on the practice of medicine as those introduced in the preceding 20 years. The figures quoted by Dr Grabau do not negate the argument. A reduction in mortality from cardiovascular, respiratory and digestive disorders would far more likely reflect the effect of drugs introduced in the preceding 20 years rather than the effect of drugs only introduced in the last 20 years. Regardless of when the drugs were introduced, other factors, such as decreased smoking, may have contributed more to the reduction.

If this argument is correct, then clearly the patent system has not achieved its aim of stimulating the development of important new drugs, so it should be reviewed. The other issues raised by Dr Grabau would presumably be considered in such a review.

Polycystic ovary syndrome

Editor, – I note that many people with polycystic ovary syndrome are being prescribed long-term metformin by their general practitioner regardless of any desire to fall pregnant.

I also note that the diagnosis of this syndrome seems to be woollier than a sheep in a lambswool jumper with ugh boots. Even the polycystic part appears to be excluded in some diagnostic criteria, because polycystic ovaries seem to be a feature of chronic anovulation regardless of cause. Yet many people attract the diagnosis on this feature alone with or without being overweight.

I recall a study showing a lack of evidence for cardiovascular risk in these patients and I find that hard to integrate with their insulin resistance. Dr Joyner correctly uses this to continue to prescribe combined oral contraceptive pill to patients over 35, but this sits uncomfortably with me. Could Dr Joyner comment on the quality of this evidence?

If such a person had a BMI > 35 then I would avoid the combined oral contraceptive pill, but this practice is independent of a diagnosis of polycystic ovary syndrome.

Kevin O'Dempsey
General practitioner
Brisbane

Dr B. Joyner, the author of the article, comments:

As mentioned in my article, polycystic ovary syndrome is a heterogeneous condition. It is a syndrome based on phenotype and there is no single diagnostic criterion. The definitions used in trials may vary depending on the feature being studied. There have also been regional variations in definitions. US definitions have focused on the endocrine features, while definitions from the UK have required the demonstration of polycystic ovaries. There was further revision of the criteria for polycystic ovary syndrome at an international consensus workshop in 2003.[1] If other causes are excluded, two of the following criteria are required:

- oligo- and/or anovulation
- clinical and/or biochemical signs of hyperandrogenism
- polycystic ovaries.

The results of studies regarding the risk of cardiovascular disease in women with polycystic ovary syndrome are conflicting. Most studies have been small and retrospective. Cohorts need to be followed for a longer period of time. However, cardiovascular risk factors including hypertension, diabetes, and hypercholesterolaemia are more common in women with polycystic ovary syndrome, a syndrome that often interweaves with the metabolic syndrome.[2,3]

As mentioned in my article, there is no evidence to suggest women with polycystic ovary syndrome experience more cardiovascular events while on the combined oral contraceptive pill. However, most of the studies have been small and short term. The use of the oral contraceptive pill therefore requires clinical judgement of the harms and benefits for each woman.

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Antibiotics for surgical prophylaxis

Editor, – I would agree that the principles set out in the article 'Antibiotics for surgical prophylaxis' (Aust Prescr 2005;28:38–40) should be applied to dento-alveolar surgery. However, the suggestions set out in the Dental notes (Aust Prescr 2005;28:41) represent a hybrid of traditional dental practice which is not in accord with current evidence-based risk-benefit assessment.

Traditionally in dental practice antibiotics have been given for the prophylaxis of impacted tooth removal after surgery has been completed.[1] This is inappropriate and contrary to the principles of surgical prophylaxis. The suggestion of giving antibiotics either orally or intravenously before the procedure is a step in the right direction, but is not widely currently followed in dentistry. It is also weakened by the suggestion that antibiotics should be continued post-extraction as a matter of clinical judgement.

Current evidence-based studies show that the actual risk of infection after third molar removal is low, of the order of 3–5%. This is similar to the risk of adverse reaction to the penicillins, which are the most commonly used antibiotics for this purpose.

In accordance with the literature, the Oral and Maxillofacial Surgery Unit in Adelaide does not give medically fit patients having dento-alveolar surgery antibiotic prophylaxis. Over the last decade, and many thousands of cases, there has been no increased incidence of infection.

This whole issue is currently being reviewed in depth and will shortly be submitted for publication in the Australian Dental Journal and in the new therapeutic guidelines for dental practitioners.

Alastair N. Goss
Professor and Director
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The University of Adelaide

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Associate Professor R.G. Woods, author of the Dental notes, comments:

I believe the views I expressed in the Dental notes are essentially consistent with the views expressed in Professor Goss' letter. However, Professor Goss and I see things from different backgrounds, Professor Goss from the Oral and Maxillofacial Surgery Unit in Adelaide and myself from general practice in a rural community.

Most third molars I remove appear to communicate, however slightly, with the oral cavity and often appear infected. The mucosal flap and surrounding soft tissues are often the site of a persistent, possibly anaerobic infection associated with eruption. Other teeth requiring removal usually have evidence of long-term infection, an apical bone lesion or loss of supporting alveolar bone.

In reference to my use of the term 'clinical judgement', essentially I refer to pre-operative assessment of the patient including consideration of the reason for the removal of the tooth, whether there is infection and such factors as immunosuppression or any other general condition which may affect recovery. It is my experience that where infection is present, although drainage is achieved by removal of the tooth, recovery is assisted by appropriate antibiotic therapy.

Varicella vaccine

Editor, –The article 'Frequently asked questions about varicella vaccine' (Aust Prescr 2005;28:2–5) notes 'there is a small potential to transmit the vaccine virus ... from direct contact with vesicles'. If a pregnant woman or immunosuppressed patient contacts the vesicles which sometimes appear on a vaccine recipient, is zoster immunoglobulin indicated?

Ina di Paola
Travel medicine
Sydney

Associate Professor Jonathan R. Carapetis, one of the authors of the article, comments:

There is no definitive answer to this very pertinent question. The main problem lies in deciding whether the rash is vaccine-associated or a potential infection with wild varicella zoster virus that happens to have occurred in the period following immunisation. If it is vaccine-associated, the risk of transmission is incredibly low. I consulted the world's leading expert on the vaccine, Professor Anne Gershon of Columbia University in New York, who informed me that so far out of over 40 million doses of vaccine distributed,

there are only four instances of transmission and all contact cases were mild. Therefore, there is no need to give varicella zoster immunoglobulin to any contact of a definitely vaccine-associated rash, whether pregnant, immunocompromised or otherwise. If a clinical illness consistent with varicella subsequently occurred in a pregnant or immunocompromised contact, it would be sensible to treat early with aciclovir.

How to decide if the rash is vaccine-associated? Most vaccine-associated rashes occur several weeks after immunisation (median about three weeks), consist of just a couple of papules or vesicles, and are not associated with systemic symptoms. If there are more than just a few lesions, or there are systemic symptoms, and especially if the rash occurs in the first week or two following immunisation, then it is more likely to be due to infection with a wild virus. If you are really uncertain, then err on the side of assuming a wild infection, and give zoster immunoglobulin to high-risk contacts, provided the exposure fits within the guidelines recommended in the Immunisation Handbook.[1]

Reference

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Isomers – correction

Editor, – I need to inform readers of a correction to the article 'Inside the isomers: the tale of chiral switches' (Aust Prescr 2004;27:47-9). On page 47 under Introduction, I cited salmeterol as a single enantiomer drug, however, it is currently marketed as the racemate – noting that the R enantiomer is the active species.

Andrew Somogyi
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Book review

Therapeutic Guidelines: Endocrinology. Version 3.

Melbourne: Therapeutic Guidelines Limited; 2004.

312 pages. Price $39, students $25.30, plus postage

Beres Joyner, General practitioner and Senior lecturer, Rural Clinical Division, School of Medicine, University of Queensland, Rockhampton, Qld.

This familiar yellow book with the metamorphosing tadpole on the cover has further matured and also experienced an expansion in girth (80 pages in three years). It has been extensively revised.

The book aims to provide 'what a clinician needs to know to manage a patient with a given condition'. For commonly encountered clinical conditions in general practice such as diabetes, obesity, thyroid disorders, osteoporosis, contraception, ovarian replacement therapy and menstrual disorders, the guidelines provide excellent summaries of current management recommendations, including drug therapies. It answers questions that arise in clinical practice. How do you choose between sulfonylureas for a person with diabetes? How do you manage hypoglycaemia in a person on acarbose? How do you monitor and adjust the dose of carbimazole for a person with thyrotoxicosis? How do you interpret bone mineral density results? When should you screen for thrombophilia in a woman who wants the combined oral contraceptive pill? What are the important drug interactions with the combined oral contraceptive pill? How do you overcome the skin irritation when testosterone impregnated adhesive skin patches are used? What happens if a woman with diabetes gets pregnant while on an ACE inhibitor?

These guidelines are well written and easy to read and there are lots of practical points. They are minimally but appropriately referenced with canonical papers. Although the style is definitive, it is not didactic. Where clinical practice is not based on evidence, this is indicated. There are a few minor errors, but these do not detract from the book overall. It represents good value for the money and will be useful for busy practising clinicians, and also medical students. Although time is a valuable resource, I would encourage general practitioners to read through the chapters on conditions they manage frequently.

Oral isotretinoin

John R. Sullivan, Dermatologist and Clinical Pharmacology, Southderm Kogarah, Central Sydney Dermatology, Liverpool Hospital and University of New South Wales, Sydney

Summary

Oral isotretinoin is listed on the Australian Pharmaceutical Benefits Scheme for patients with severe cystic acne that has failed to respond adequately to other therapy. A single course of isotretinoin induces a long-term remission in over 80% of these patients. A minority, usually after a prolonged remission, benefit from a subsequent course. Pregnancy prevention is of paramount importance for women taking isotretinoin as it is highly teratogenic. Extra caution is also needed if the patient has diabetes, hyperlipidaemia or a mood disorder, drinks heavily or has a very physically active lifestyle.

Key words: acne, adverse effects, birth defects.

(Aust Prescr 2005;28:59–61)

Introduction

Cystic acne is characterised by numerous painful nodules that if inadequately controlled result in permanent scars. The natural duration of severe cystic acne is at least 10 years. Sufferers often become increasingly self-conscious, and many even isolate themselves to avoid social interactions. The impact of severe acne and its scars can be psychologically devastating in our increasingly appearance-conscious society. This is not just a disease of youth. Employers are less likely to recruit people with severe cystic acne and if working, these individuals are less likely to apply for and get promotions. Severe acne can erode a person's self-confidence and may diminish their chances of finding a partner because of fear of rejection due to their appearance.

Isotretinoin, a retinoid related to vitamin A, is an effective oral treatment for patients with severe cystic acne. Isotretinoin reduces sebum production, unblocks pores and stops formation of new comedones. By opening up the hair follicle, it also reduces the anaerobic bacteria that contribute to the inflammation seen in acne. It is not effective on pre-existing scars and should ideally be started before scarring has begun. As isotretinoin has some serious adverse effects, it can only be prescribed by dermatologists. Early referral to a dermatologist should be considered for patients with progressively worsening, moderately severe acne or a family history of severe cystic scarring acne.

Dosing, duration of therapy and total dose

Australian dermatologists usually prescribe a low starting dose then slowly escalate it over a few months (usually to 0.5–1 mg/kg/day but varying with patient tolerance and response). This reduces the risk and severity of adverse reactions including most mucocutaneous adverse effects, severe acne flares, and transient increases in liver enzyme concentrations. The incidence and severity of most adverse effects appear to be dose related, peak within weeks of dose increments and then generally improve as the body adapts and patients get used to taking extra skin and mucosal care, and other precautions.

Facial acne generally improves first, then the neck, back and finally buttocks. In Australia the total dose of isotretinoin given over 5–8 months is approximately 120 mg/kg. A longer course and higher total dose might be prescribed for clearing and inducing a remission in particularly severe cases of acne conglobata that extend to the lower back, buttocks or thighs. The product information recommends a 16-week course. Most Australian dermatologists prefer to give a longer course at a lower dose to improve tolerance and the outcomes for patients.

Isotretinoin is a potent teratogen

In most pregnancies exposure to oral isotretinoin causes severe birth defects. Even babies born without obvious central nervous system abnormalities may be mentally retarded. Every reasonable precaution must be taken to ensure female patients are not, nor become, pregnant while taking isotretinoin. Although isotretinoin and its metabolites are not stored in the body and are eliminated within a week of stopping therapy, effective birth control is necessary from one month before the start of treatment until one month after the end of treatment. Patients cannot donate blood during, and until a month after, treatment because of this risk. There are no risks to the fetus however if the father is taking isotretinoin.

Oral isotretinoin causes severe birth defects

There are important implications for the patient, their family, general practitioner, prescribing dermatologist, and pharmacist. Female patients should be using at least one effective contraceptive measure reliably and have a recent negative pregnancy test before starting therapy. Isotretinoin is then started on the second or third day of the next menstrual period.

Regular reviews of females of childbearing potential taking isotretinoin may include pregnancy testing along with further counselling about the importance and adequacy of contraception. The frequency of these reviews is tailored according to the perceived risk of pregnancy, the precautions in place and the patient's reliability in using them. Teenagers and young adults may require extensive counselling to correct misbeliefs on the effectiveness of and the best and safest ways to use contraception.

I discourage patients from purchasing isotretinoin via internet or mail order pharmacies as there is no opportunity for regular extra face-to-face reminders about the damaging effects of isotretinoin in pregnancy.

If a female taking isotretinoin suspects that she might have become pregnant, she should stop the medication immediately and seek urgent medical advice and pregnancy testing along with expert counselling.

Common adverse effects

Most adverse effects are dose related and due to the inhibition of sebaceous and meibomium gland function and/or the premature desquamation of epidermal cells. This leads to drying of the skin and mucous membranes and their increased sensitivity to irritation. Before starting isotretinoin, the patient should be given a long list of recommended changes to make in their personal care and lifestyle to minimise the risk of the drug causing symptoms or adverse effects (Table 1). Some patients are excellent at following recommendations while others wait until they have problems before taking corrective measures.

A flare of acne several weeks into therapy unfortunately does occur in a minority of patients. This is less common and less severe if the dose is started low then slowly escalated. A patient with an acne flare worse than their usual flares in the first weeks or months after starting isotretinoin should be seen urgently by their dermatologist. A short course of prednisolone might be prescribed, possibly in conjunction with oral erythromycin and triamcinolone injections into cysts.

Isotretinoin and the liver

Unlike vitamin A, isotretinoin is not stored in the liver. Isotretinoin is probably not directly hepatotoxic. When isotretinoin is started at higher doses (for example 1 mg/kg/day) 'transient leaky hepatocyte membranes' are thought to be responsible for the asymptomatic rise in liver enzymes in a small proportion of patients. This is uncommonly seen in Australia when a lower starting dose is used. If liver enzymes rise more than two and a half fold above normal or they fail to normalise when rechecked 3–4 weeks later, investigations for other causes (such as viral hepatitis, alcohol) are indicated. Consideration should still be given to stopping isotretinoin, because it can exacerbate liver enzyme rises due to other causes. Patients need counselling regarding alcohol intake and the avoidance of other hepatotoxins while taking isotretinoin and for several weeks after its cessation.

Table 1

Recommended methods of minimising the adverse effects of isotretinoin

Problem	Solution
Common problems	
Dry cracked lips	Lip balm always in pocket, pawpaw ointment at night if very dry
Dry skin (especially face)	Soap-free wash, non-fragranced, plus non-acnegenic moisturiser
Sun sensitivity	SPF 30 broadspectrum sunscreen, a hat and appropriate clothing if outdoors (10 am to 3 pm)
Dry or irritable eyes	Artificial tears
Contact lens intolerance	Wear glasses
Eczema	Moisturise regularly, intermittent topical corticosteroids
Dry cracked nose/nose bleeds	Petrolatum or vitamin E lotion twice a day applied using cotton tip
Less common/occasional but more significant problems	
Angular cheilitis	Mupirocin ointment or povidone-iodine qid (usually due to *Staphylococcus aureus* infection)
Impaired night vision	Avoid night driving or check adequacy of vision before driving at night
Visual disturbance	Refer for ophthalmological examination and consider ceasing treatment
Paronychia	Nails should extend beyond lateral fold and not have sharp edges. Topical povidone-iodine, anti-staphylococcal antibiotics
Skin fragility and delay in wound healing	Avoid waxing, avoid and/or take extra protective precautions for activities associated with significant hand trauma e.g. manual labour tasks
Tiredness, tenderness or stiffness of bones, joints and muscles	These vary greatly between patients, and are dose- and activity-related (improve or resolve with activity modification and/or dose reduction over days to weeks). Avoid extremely strenuous activities; exercise to maintain conditioning, use isotretinoin in the off-season for serious sports enthusiasts/professional athletes. May also unmask underlying problems e.g. lower backache.

Isotretinoin and blood lipids

There is a small increase in triglyceride concentrations in 25% of patients and 7% have an increase in their cholesterol concentrations. These changes resolve on stopping therapy. Extra caution needs to be taken in patients with high baseline lipid concentrations, a family history of hyperlipidaemia,

diabetes, or who drink large amounts of alcohol. These patients may have larger increases in their triglyceride concentrations when taking isotretinoin and require monitoring of their lipids with each dose increase.

There are a number of reports of a large rise in triglycerides (for example, greater than 10 mg/L) being associated with symptomatic steatohepatitis and acute pancreatitis. Many of these reactions may have been prevented by measuring baseline lipids and then repeating them on at least one occasion several weeks into therapy. These tests should be repeated regularly during therapy and appropriate action taken if a significant rise occurs.

Isotretinoin can reveal individuals who have an increased risk of developing early onset hyperlipidaemia, insulin resistance, obesity and accelerated atherosclerosis. Those at greatest risk are teenagers and young adults whose triglyceride and cholesterol increase significantly while on isotretinoin. After completing a course of isotretinoin these people will benefit from regular monitoring of their metabolism, education about healthy living and early preventative health interventions.

Rare idiosyncratic but important reactions

People starting isotretinoin often have a few minor, transient headaches during the first few weeks of therapy. However, if these headaches occur on waking and are persistent or severe, or are associated with nausea and vomiting or blurred vision, suspect pseudotumour cerebri. Isotretinoin needs to be promptly stopped and the patient should be examined for papilloedema. An urgent referral to a neurologist for further assessment and management is indicated.

There are rare reports of reversible cytopenias occurring in people taking isotretinoin. Check for cytopenia if a patient presents with high fever, sore throat, petechiae or easy or unusually severe bruising.

Acne, isotretinoin and depression

Severe cystic acne is associated with an increased risk of depression. It occurs relatively commonly in males in their late teens and early twenties – a group known to be at relatively high risk of depression, suicide and first developing schizophrenia. If acne flares after several weeks of taking a drug described as the last resort for severe acne or if the adverse effects of a dry, red face with cracked lips are particularly severe, patients may have justifiable reasons for feeling down about their acne and its therapy. All patients being seen for acne and particularly more severe forms of acne should therefore be routinely screened for symptoms of depression whenever seen by a health professional.

While there are a number of media reports, there is no proven link between isotretinoin and depression, suicide or psychotic symptoms. So far, studies and analysis of spontaneous reports suggest that, overall, isotretinoin may have a protective effect against depression. There is a tendency for patients' mood to elevate as their acne improves and clears. However, these reports cannot exclude a rare idiosyncratic susceptibility to psychiatric illness and this issue should be discussed when patients give informed consent to treatment.

If a patient with severe cystic acne has a past history of depression or is suspected or diagnosed as depressed, they should be closely monitored and managed in conjunction with their general practitioner or psychiatrist before starting isotretinoin. Depression does not preclude the prescribing of isotretinoin particularly if the patient's acne is responsible for their lowered mood. Their mood will not necessarily worsen while on isotretinoin and may even elevate with successful control of their acne.

Conclusion

Isotretinoin is the gold standard treatment for severe cystic acne, but there is a major risk of harm associated with its use. This risk can be reduced by careful assessment of the patients before and during treatment. Patients, particularly women, need to be informed about the adverse effects of isotretinoin and how to avoid them.

Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

1. Women taking isotretinoin should avoid pregnancy until at least one month after stopping treatment.
2. Patients taking isotretinoin require regular testing of their liver function.

Management of acute bleeding in the upper gastrointestinal tract

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Summary

Acute upper gastrointestinal haemorrhage is common. Patients require simultaneous resuscitation and clinical assessment followed by referral for endoscopy. There have been significant developments in terms of the acute endoscopic and medical treatment of upper gastrointestinal haemorrhage, as well as the development of prognostic tools to help guide management. Preventing recurrent haemorrhage is also important. This requires an understanding of both the aetiology and risk factors for recurrence, as well as the medical and endoscopic treatments available to reduce these risks.

Key words: peptic ulcer, varices, endoscopy, haemorrhage.

(Aust Prescr 2005;28:62–6)

Introduction

Acute upper gastrointestinal haemorrhage (bleeding proximal to the duodenojejunal flexure) is a common medical emergency (170 per 100 000 adults annually). Although its incidence may be declining, the mortality rate of upper gastrointestinal haemorrhage remains high, approximately 6–8%.[1] Depending on the site and rate of bleeding, a patient may present with melaena (black, tarry stool), haematemesis (vomiting 'coffee-grounds' or fresh blood), haematochezia (red blood per rectum) or syncope. Melaena may also result from bleeding into the more distal small intestine or proximal colon.

The majority of patients with upper gastrointestinal haemorrhage require hospital management. General practitioners have an important role in assessing and resuscitating patients and then managing them following discharge to reduce the risk of recurrent bleeding.

Initial assessment

Initial clinical assessment is directed towards the haemodynamic stability of the patient and the requirement for immediate resuscitation.

History

The presenting symptom, past medical history and current medications are important for establishing the aetiology (see box and Table 1) and severity of haemorrhage. A history of recent dyspepsia, or use of aspirin or another non-steroidal anti-inflammatory drug (NSAID) may suggest a bleeding ulcer. The presence of chronic liver disease raises the possibility of variceal haemorrhage.

Common causes of upper gastrointestinal haemorrhage

- peptic ulcer disease
- gastric erosions
- oesophagitis
- oesophageal or gastric varices
- emetogenic injury (Mallory-Weiss tear)
- malignancy
- angiodysplasia

Table 1

Drugs associated with gastrointestinal haemorrhage

Drugs	Mechanism
Aspirin and non-steroidal anti-inflammatory drugs, including COX-2 inhibitors	Mucosal toxicity
Prednisolone	
Warfarin	Impaired haemostasis
Clopidogrel and other antiplatelet drugs	
Aspirin	
Heparin (both fractionated and unfractionated)	
Selective serotonin reuptake inhibitors	

Haematemesis that follows prolonged vomiting or retching may be the result of a Mallory-Weiss tear. A history of syncope may reflect haemodynamically significant bleeding. Vomiting frank blood suggests severe haemorrhage from an arterial or variceal source. In contrast, 'coffee-grounds' emesis is unlikely to reflect active bleeding.

Approximately 50–100 mL of blood is needed to produce melaena. Haematochezia may occur with brisk upper gastrointestinal haemorrhage and is usually accompanied by haemodynamic compromise.

Examination

It is critical to assess the patient's haemodynamic status by measuring heart rate, blood pressure and postural changes. In haemodynamically compromised patients a fall in blood pressure may follow only a minor change in posture, for example from lying flat to sitting at a 45° incline. Variceal haemorrhage is more likely if stigmata of chronic liver

disease are present, particularly if there is evidence of portal hypertension, for example ascites and splenomegaly. An ulcer may cause epigastric tenderness. Digital rectal examination is important to confirm the presence of true melaena.

Investigations

Haemoglobin needs to be measured in all patients but may initially underestimate true blood loss, due to delayed haemodilution of the vascular space. Blood should be sent urgently to transfusion services for cross-matching. Other important tests include platelet count, urea:creatinine ratio, coagulation indices and liver function tests including albumin. Patients with end stage liver disease may have normal liver enzymes, yet have impaired synthetic liver function as evidenced by low albumin, or reduced clotting factors.

Risk assessment scores

The Blatchford score predicts the need for therapy and thus admission. Patients are unlikely to need treatment and therefore may not require admission if they satisfy the following criteria:

- urea less than 6.5 mmol/L
- haemoglobin greater than 130 g/L (men) or 120 g/L (women)
- systolic blood pressure greater than 110 mmHg
- pulse less than 100 beats per minute (excluding those with syncope).

This 'fast-track' triage could be used in an emergency department to avoid unnecessary admissions.[2] Likewise in regional areas, such a scoring system could help the general practitioner decide if a patient requires immediate transfer to a tertiary referral centre, or whether it is reasonable to discharge the patient with a view to arranging an early outpatient endoscopy at the closest facility. The safety of using the management algorithm in this way is yet to be formally evaluated, and thus patients should continue to be managed on a case by case basis.

The Rockall score is frequently used for risk categorisation (Table 2). The score is the sum of each component, calculated before and after endoscopy. This predicts rates of re-bleeding and mortality and can be used in management algorithms, for example whether to admit a patient to an intensive care unit. Post-endoscopy risk scores of 2 or less are associated with a 4% risk of re-bleed and 0.1% mortality. In one study about 30% of patients had post-endoscopy risk scores of 2 or less and thus significant health savings could be achieved by early endoscopy and discharge.[3]

Resuscitation

Until cross-matched blood is available, resuscitation proceeds with crystalloid or colloid solutions aiming for a systolic blood pressure of greater than 100 mmHg. Thiamine replacement should be considered when there is a history of alcohol abuse.

Table 2

Rockall score for the prognostication of upper gastrointestinal bleeding [3]

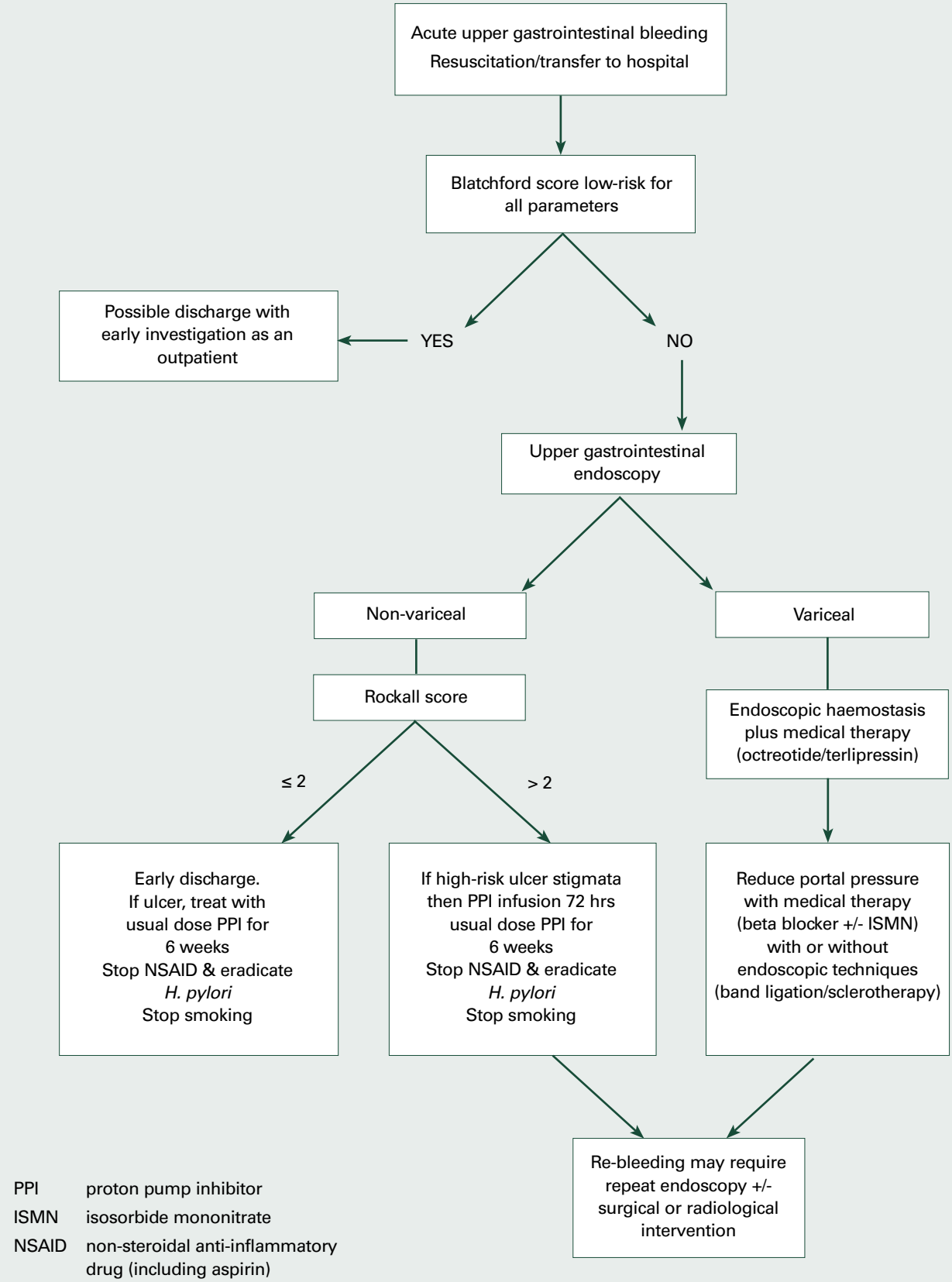
	Score			
	0	1	2	3
Pre-upper gastrointestinal endoscopy				
Age	<60 years	60–79 years	≥80 years	
Shock	*No shock* BP >100 mmHg and pulse <100	*Tachycardia* BP >100 mmHg and pulse >100	*Hypotension* BP <100 mmHg	
Comorbidity	No major comorbidity		Ischaemic heart disease, cardiac failure, any major comorbidity	Renal or liver failure Disseminated malignancy
Post-upper gastrointestinal endoscopy				
Diagnosis	Mallory-Weiss or no lesion found, and no major stigmata of recent haemorrhage	All other diagnoses	Gastrointestinal malignancy	
Major stigmata of recent haemorrhage	None or dark spot only		Blood in upper gastrointestinal tract, non-bleeding visible vessel, spurting vessel or adherent clot	

BP systolic blood pressure

Patients with a score of 0, 1 or 2 have a lower risk of haemorrhage, whereas approximately 50% of patients with a post-endoscopy score of 8 or more will re-bleed.

Fig. 1

Management of acute upper gastrointestinal haemorrhage



PPI proton pump inhibitor
ISMN isosorbide mononitrate
NSAID non-steroidal anti-inflammatory drug (including aspirin)

The target haemoglobin concentration is contentious. Some advocate 70–80 g/L for otherwise healthy individuals, without active bleeding, who are haemodynamically stable.[4] In patients older than 65 or those with cardiovascular disease a target concentration of 90–100 g/L may be more appropriate.

Endoscopy – diagnosis and management

After resuscitation an endoscopy is arranged. Some patients with profuse haemorrhage require emergency endoscopy, however the majority can be scheduled on the next routine list. The endoscopy should, however, take place within 24 hours of presentation, both to guide management and to facilitate the early discharge of patients with a low risk of recurrent bleeding.

When high-risk lesions are seen (ulcers with active spurting vessel or non-bleeding visible vessel) endoscopic therapy significantly reduces re-bleeding rates and mortality.[1] A dual-modality endoscopic approach is currently recommended, with a combination of (1:10 000) adrenaline injection and thermal coagulation.

Band ligation and sclerotherapy are the two main endoscopic techniques for treating acute oesophageal varices.[5] These procedures are less successful in gastric varices, although injection with tissue adhesive may be effective.

Medical management of upper gastrointestinal bleeding (Fig. 1)

Non-variceal

In gastrointestinal haemorrhage there is enhanced mucosal fibrinolytic activity, impairing haemostasis.[6] Suppressing acid secretion blunts this escalation in fibrinolysis. In this setting high-dose proton pump inhibitor therapy reduces the risk of recurrent bleeding.[7]

Proton pump inhibitor therapy can be administered parenterally (either intermittently or by infusion) or orally. When high-risk features are present at endoscopy it may be advisable to administer high dose intravenous proton pump inhibitor therapy, that is omeprazole 80 mg (or equivalent) bolus followed by an infusion rate of 8 mg/hour for 72 hours. Where the cost of intravenous proton pump therapy is prohibitive and especially when there are no high-risk ulcer features, an oral proton pump inhibitor may be satisfactory.[7]

Variceal

Medical therapy reduces variceal bleeding by lowering portal venous pressure. The available drugs include vasopressin and its synthetic analogue terlipressin, as well as somatostatin and its synthetic analogues octreotide and vapreotide. The relative merits of these drugs are unclear. The addition of an octreotide infusion to endoscopic therapy improves bleeding control and reduces transfusion requirements[5], therefore a combination of endoscopic and medical treatment is probably the best approach. However, only terlipressin has been shown to reduce mortality rates following variceal bleeding[8], but it is currently only available in Australia under the Special Access Scheme.*

It is important to remember that variceal haemorrhage may precipitate hepatic encephalopathy. Re-bleeding from varices or ulcers may require repeat endoscopy. Sometimes endoscopic therapy is unsuccessful and surgery is needed.

Prevention of recurrent bleeding

Non-variceal

Prevention of recurrent bleeding in ulcer disease should be directed towards the underlying cause. All patients should be asked about aspirin and other NSAID use and be tested for *Helicobacter pylori.* Patients who smoke should be advised to stop.

NSAID-induced ulcers

NSAIDs should be discontinued where possible. The ulcer may then be healed with an H_2-receptor antagonist or a proton pump inhibitor over a period of six weeks.[9] Current clinical practice favours proton pump inhibitor therapy over H_2-receptor antagonist for ulcer healing. No further endoscopy is required for duodenal ulcers, but repeat endoscopy at eight weeks is advisable for gastric ulcers to ensure healing and exclude malignancy.

In patients requiring ongoing NSAID therapy, a concomitant proton pump inhibitor achieves a greater rate of ulcer healing than H_2-receptor antagonists.[10] An alternative approach is to substitute paracetamol or a COX-2 selective drug for the conventional NSAID. In terms of the rate of recurrent bleeding, this strategy is comparable to taking a conventional NSAID with a proton pump inhibitor.[11] The rate of recurrent haemorrhage in this group, however, is still relatively high. It is important to remember that the gastrointestinal advantages of COX-2 selective inhibitors are negated by concomitant aspirin therapy, and that there has been recent concern about the cardiovascular safety of this class of drug. A proton pump inhibitor reduces the risk of recurrent bleeding when long-term aspirin therapy is required. The timing of the resumption of a medication which may have contributed to the gastrointestinal haemorrhage should balance the likelihood of re-bleeding, the indication for the drug and whether safer alternatives are available.

H. pylori-associated ulcers

All patients with ulcer disease should be tested for *H. pylori*[12] and the bacteria eradicated if found. Successful eradication, usually a seven day regimen of triple therapy, significantly reduces the risk of ulcer recurrence.[13] Once *H. pylori* eradication is confirmed and the ulcer has been healed by six weeks of treatment with an H_2-receptor antagonist or proton pump inhibitor, no further therapy is required.

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* http://www.tga.gov.au/docs/html/sasinfo.htm [cited 2005 May 10]

Idiopathic ulcer

A number of patients have ulcers without a clear aetiology. These patients should have their ulcers healed with either an H_2-receptor antagonist or a proton pump inhibitor for 6–8 weeks.[9] However, they may require long-term acid suppression.

Variceal

Variceal bleeding recurs in approximately two-thirds of patients.[5] Both endoscopic and medical strategies are used in an attempt to reduce recurrent oesophageal variceal bleeding. Regular endoscopic treatment, usually 3–4 sessions (initially weekly, then every 2–3 weeks), with either sclerotherapy or banding can obliterate oesophageal varices. Band ligation is preferred because of greater efficacy and a lower incidence of oesophageal strictures.[5] Alternatively, reducing portal pressure with a non-selective beta blocker (propranolol, nadolol (not approved in Australia)) with or without a long-acting nitrate has proven effective. The combination of nadolol and isosorbide mononitrate therapy was superior to band ligation alone in preventing recurrent variceal bleeding.[14] It is possible, however, that combination endoscopic and medical therapy (in this study the medical treatment was nadolol and sucralfate) may be more effective than either alone.[15] Some patients require specialist techniques such as porto-systemic shunting by surgery or by a transjugular intrahepatic porto-systemic shunt. Other patients may not be able to have optimal medical treatment because of contraindications or adverse effects. In the case of alcoholic liver disease, failure to stop drinking increases the risk for recurrent haemorrhage, so abstention from alcohol is critical.

Conclusion

Management of acute upper gastrointestinal haemorrhage begins with clinical assessment and resuscitation. Endoscopy is required for diagnosis and initial therapy. A combination of medical and endoscopic strategies are used to reduce the risk of recurrent bleeding.

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Associate Professor Fraser has received unrestricted grants from AstraZeneca, Pfizer, Lederle, and Altana, and acts as a consultant to Pfizer. Dr Worthley has received travel grants from AstraZeneca.

Self-test questions

The following statements are either true or false (answers on page 79)

3. Acute treatment with high doses of proton pump inhibitors reduces the risk of further bleeding after an upper gastrointestinal haemorrhage.
4. A patient needs to lose at least 500 mL of blood into the gut before they develop melaena.

Pharmacological treatment of behavioural problems in dementia

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Summary

Dementia is commonly associated with distressing behavioural problems that warrant intervention. A general medical assessment of the patient is needed before assessing whether specific treatment is required. Both non-pharmacological and pharmacological interventions can be considered. The best available evidence is for the use of low-dose antipsychotic medication in patients with agitated or aggressive behaviour with or without associated psychotic symptoms. There is less evidence to support the use of antidepressants, anticonvulsants and cholinesterase inhibitors in patients whose dementia is complicated by behavioural problems. When psychotropic medication is prescribed to people with dementia, it should be regularly reviewed with a view to stopping it or assessing the patient after a trial off the medication.

Keywords: antipsychotics, antiepileptics, antidepressants.

(Aust Prescr 2005;28:67–70)

Introduction

Dementia is a clinical syndrome usually characterised by progressive cognitive impairment, neuropsychiatric symptoms, impaired capacity to undertake activities of daily living, and behavioural disturbance. It affects approximately 6% of Australians aged 65 years and over and is the second greatest cause of years of life lost due to disability in Australia. More than 160 000 Australians suffer from dementia and many other family members and friends are indirectly affected. The commonest cause of the dementia syndrome in Australia is Alzheimer's disease.

Behavioural and psychological symptoms of dementia

A number of terms are used interchangeably to refer to the behavioural or psychological symptoms of dementia. These include neuropsychiatric symptoms of dementia, non-cognitive symptoms of dementia, behavioural and psychological symptoms of dementia and behavioural disturbance in dementia.

Neuropsychiatric symptoms such as apathy, anxiety, agitation, depression, delusions and hallucinations occur commonly in older people with dementia. These symptoms are a major cause of personal distress to patients and their families and place a substantial burden on the healthcare system. Neuropsychiatric symptoms are more important predictors of caregiver burden than cognitive impairment and are associated with admission to a nursing home. The prevalence of behavioural symptoms in hostel and nursing home populations is much greater than in older people living in the community.

The best available estimates of the prevalence of neuropsychiatric symptoms in an epidemiologically derived sample of older people with dementia living in the community come from the US Cache County Study.[1] Across all categories of severity, 61% of patients had one or more neuropsychiatric symptoms and 32% had severe symptoms. The most prevalent individual symptoms were apathy (27.4%), depression (20.1%), irritability (20.4%), aggression/agitation (23.7%) and delusions (18.5%).

Important assessment and management principles

Take a personal history from the patient and an informant to better understand their symptoms in the context of their previous experiences. Before embarking on symptomatic treatment for behavioural problems in people with dementia, it is important to assess the patient's general health. There may be an underlying remediable cause for the symptoms.

Other illnesses

The development of acute agitation in people with dementia is often due to delirium, which is commonly precipitated by intercurrent illness or polypharmacy. Common causes of delirium include infections of the urinary tract, respiratory tract or skin, overzealous use of drugs with anticholinergic properties, and inappropriate use of hypnosedatives. Treatment should be directed towards the underlying cause, although short-term symptomatic treatment for the behavioural symptoms may be required.

In some patients with moderate or severe dementia, the development of agitated behaviour may indicate unreported pain from conditions such as osteoarthritis. If the doctor suspects this possibility, a time-limited therapeutic trial of simple

analgesia such as regular paracetamol should be considered. Although case series have reported the use of narcotic analgesics in this situation, there is insufficient evidence to recommend this approach.

In some older people with dementia, the development of a comorbid depressive, anxiety or psychotic disorder may present with abnormal behaviour. The diagnosis of such conditions in the presence of more than mild dementia can pose a clinical challenge.

Drugs

Although drugs are often used in the management of behavioural problems in older people with dementia, it is important to review the medications they already take before adding more. Sometimes behavioural problems are caused by sub-acute delirium or other types of toxicity due to prescribed medication. Drugs that are particularly prone to cause behavioural problems in older people include those with anticholinergic properties (tricyclic antidepressants such as amitriptyline, phenothiazine antipsychotics such as chlorpromazine, and anti-Parkinsonian drugs such as benztropine), benzodiazepines such as diazepam, and narcotic analgesics such as tramadol. It is often possible to cease some medications in older people without adverse consequences. In residential aged-care settings a review of the patient's medication in consultation with a clinical pharmacist may be useful.

Environment

The prudent prescriber assesses the patient's environment and the capacity of the patient's caregivers to cope with the behavioural problem. Abnormal behaviour in people with dementia often comes to clinical attention because of a mismatch between the patient, their environment and the characteristics of the caregivers. Sometimes a change in the environment or caregiver behaviour will result in substantial improvement in the patient's behaviour or a better match between the patient's needs and the capacity for those needs to be met. The use of psychotropic medication may then be unnecessary.

A change in environment may be something as straightforward as changing from bathing to showering, or changing from showering in the morning to showering in the evening, or changing to a different person assisting with showering. It is useful to place familiar objects around people with dementia in an attempt to make the unfamiliar seem familiar.

Impact of behaviour

It is worth considering whether the behavioural disturbance is causing the patient obvious distress or making it difficult for others to care for them. If there is no underlying reversible cause and the behaviour is not particularly problematic, it might be worth considering a further period of observation without treatment. Hallucinations are one example of a symptom that does not always warrant treatment. The routine prescription of psychotropic medication in the absence of good general care of patients with dementia is likely to lead to further agitation and complications like confusion and falls.

Non-pharmacological approaches

A wide range of non-pharmacological interventions has been tested in behaviourally disturbed people with dementia. Many of the trials have had significant methodological limitations. Nevertheless, a recent systematic review found that there was evidence to support the efficacy of activity programs, music, behaviour therapy, light therapy, carer education and changes to the physical environment.[2] In well-run residential aged-care facilities some of these techniques are in routine use.

Interventions for patients with dementia and behavioural problems should be individualised. Specific discussion of this complex issue is contained in a report to the Commonwealth Department of Health and Ageing on the psychosocial approaches to challenging behaviour in dementia.[3]

Pharmacological approaches

When non-pharmacological approaches are insufficient to manage the patient's behaviour, drugs can be added to their treatment. It is important to consider the likely benefits against the likelihood of adverse effects and drug interactions.

Antipsychotics

There is some evidence for the efficacy of both typical (e.g. haloperidol) and atypical (e.g. risperidone[4], olanzapine[5]) antipsychotic drugs in the treatment of psychotic symptoms in people with dementia. There is also some evidence for the use of these drugs in people with dementia who are aggressive or agitated but who do not have overt psychotic symptoms.

Although the so-called atypical antipsychotic medications (risperidone, olanzapine, quetiapine, amisulpride, aripiprazole) have safer adverse effect profiles than typical antipsychotic medications, most of them are not subsidised by the Pharmaceutical Benefits Scheme (PBS) for people with dementia in the absence of schizophrenia. The best evidence is for low-dose risperidone, which has been approved for the management of behavioural disturbance in dementia. The usual starting dose of risperidone in older people with dementia is 0.25–0.5 mg daily, with the final dose generally 1–2 mg per day.

A Cochrane review found that haloperidol was useful for aggression, but not for other aspects of agitation in people with dementia.[6] If haloperidol is to be used in the treatment of either psychotic symptoms or agitation/aggression, it is important to use the lowest effective dose. The usual starting dose of

haloperidol in older people is 0.5 mg daily, with the final daily dose generally 1–2 mg per day.

If either haloperidol or an atypical antipsychotic drug is used, it is important to titrate the dose slowly and check the patient frequently for adverse effects. The most important adverse effects in older patients are Parkinsonism, confusion and postural hypotension. Parkinsonism can develop after several weeks of treatment and may present with falls. At these doses, akathisia is a much less frequent problem than when higher doses are used.

When starting an antipsychotic drug in older people with dementia, it is important to have a stopping rule. Prescribe treatment for no longer than 3–6 months before tapering the dose and undertaking a trial of ceasing the medication. Patients should be regularly reviewed because their behavioural problems may abate as their dementia progresses.

Recently, concern has arisen about an increased risk of cerebrovascular adverse effects when risperidone or olanzapine are used to treat psychotic or behavioural symptoms in older patients with dementia. Although no prospective studies have been designed specifically to examine this outcome, pooled secondary analyses of randomised controlled trials suggest that both drugs are associated with a small but significantly increased risk of cerebrovascular adverse effects.[7,8] In contrast, a retrospective cohort study did not find a statistically significant increased risk of stroke when risperidone and olanzapine were compared with conventional antipsychotic medications in older people with mixed diagnoses.[9] It is not known whether haloperidol, quetiapine, amisulpride or aripiprazole are also associated with cerebrovascular adverse effects. Nor is it known whether the observed increased risk of cerebrovascular adverse effects also affects older patients with psychotic disorders but no dementia. It is therefore important to recognise that there is an increased risk in prescribing antipsychotics in these situations, so the harms and benefits should be clearly identified and discussed in as much detail as possible with the patient and their carers.

Antidepressants

Depression and anxiety symptoms occur commonly in people with dementia. Sometimes these symptoms are short-lived and do not require specific treatment. However, if the person with dementia develops a clinically significant depressive or anxiety disorder they should be treated.

Modern antidepressant medication is effective against both depressive and anxiety disorders, although the evidence base in patients with dementia is weak. The adverse effect profiles of sertraline, citalopram, escitalopram and moclobemide make them suitable for use in older people, including those with dementia. Evidence is best for sertraline, for which the usual starting dose in this patient group is 25 mg daily.[10] Treatment, if effective, should usually continue for about 12 months, or longer if there is a history of recurrent depression.

There is a risk of hyponatraemia with antidepressants in older people.[11] The prescriber should check the patient's serum sodium before and approximately one week after starting treatment with an antidepressant. However, hyponatraemia can occur several weeks into therapy, so a high index of suspicion should be maintained. Increasing confusion is a common symptom of hyponatraemia in older patients. Hyponatraemia seems to be more common in women, in patients with cerebrovascular disease, and in patients on diuretics.

Anticonvulsants

Carbamazepine and sodium valproate have been used in the management of agitated behaviour in people with dementia. The evidence base is rather weak for both drugs, although does tend to favour carbamazepine[12], despite its relatively greater propensity for adverse effects, including drug-drug interactions. Like antipsychotic treatment, anticonvulsants should only be prescribed for a limited time.

Cholinesterase inhibitors

There are preliminary data showing that some patients with dementia-related behavioural disturbance benefit from treatment with cholinesterase inhibitors. These data are based mainly on subsidiary analyses of studies designed for other purposes. Prescribers should be aware, however, that cholinesterase inhibitor treatment is sometimes associated with deterioration in behaviour. Also, there are no independent head-to-head studies comparing donepezil, rivastigmine and galantamine in the treatment of neuropsychiatric or behavioural symptoms in dementia.

Benzodiazepines

Benzodiazepines should be avoided in older people with dementia. Benzodiazepines impair cognition (particularly memory), gait (leading to falls) and, like all sedatives, may also worsen the common clinical problem of constipation. If a benzodiazepine is prescribed for severe anxiety, it should not be continued for more than two weeks. Benzodiazepines should not be used to treat insomnia in people with dementia.

Management of aggression

Physical aggression is common in dementia, particularly towards caregivers. Sometimes aggression can be managed by modifying the behaviour of the caregiver or by modifying the environment in some other way. However, pharmacological intervention is often required, particularly when there is a risk of physical injury to the patient or their carer.

In an emergency, aggressive behaviour in a patient with dementia may need to be treated with antipsychotic medication. If oral treatment is feasible, risperidone or haloperidol should

be tried. If parenteral treatment is required, the short-term use of intramuscular haloperidol or olanzapine is often appropriate. It is particularly important that following the administration of parenteral antipsychotic medication, the patient with dementia is monitored for an extended period. Adverse effects including excessive sedation and extrapyramidal reactions may occur.

The dose of antipsychotic medication should vary according to the size, gender, age and general condition of the patient. Intramuscular haloperidol is often administered in an initial dose of 1–2 mg and intramuscular olanzapine in an initial dose of 2.5 mg. Repeated dosing is sometimes required, but increases the risk of adverse effects.

Although approved for behavioural problems, intramuscular olanzapine is not currently subsidised by the PBS. Droperidol and midazolam are not recommended for use in older people with dementia. A combination of parenteral benzodiazepines with parenteral antipsychotic medication can lead to excessive sedation in older people and is not recommended for routine use.

If physical aggression is more chronic in nature and associated with other agitated behaviour, a trial of anticonvulsant medication, either sodium valproate or carbamazepine, is often appropriate. In this situation, these anticonvulsants may be used as antipsychotic sparing medications.

Ethical considerations

In most jurisdictions treatment without consent has been dealt with by statute law and a list of substitute decision makers is specified. In certain circumstances referral to a guardianship board (or similar local body) may be prudent, or even required, before treatment without consent can proceed.

In emergencies, particularly where physical violence to self or others is concerned, the doctor's duty of care might override the requirement of informed consent. Although not yet universal, in some jurisdictions patients with dementia are covered by the local Mental Health Act.

Acknowledgement: Dr David Lie provided valuable comments on an earlier draft of this article.

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Dr Byrne has been a member of national advisory committees on donepezil (Pfizer), rivastigmine (Novartis), and galantamine and risperidone (Janssen-Cilag).

See **Patient Support Organisation: Alzheimer's Australia** on page 72.

Self-test questions

The following statements are either true or false (see answers on page 79)

5. Altered behaviour in a patient with dementia may be the result of an intercurrent illness.
6. If an antipsychotic drug is prescribed to control behaviour problems in a patient with dementia, its use should be reviewed as the dementing condition changes.

NPS RADAR
Rational Assessment of Drugs and Research

The National Prescribing Service (NPS) produces RADAR (Rational Assessment of Drugs and Research) to inform people about changes to the Pharmaceutical Benefits Scheme (PBS). This is an abridged version of a RADAR comment. For the full comment on this drug, go to www.npsradar.org.au

Risperidone (Risperdal) for behavioural disturbances in dementia

PBS listing

Risperidone has been PBS-listed as an authority item for behavioural disturbances characterised by psychotic symptoms and aggression in patients with dementia where non-pharmacological methods have been unsuccessful. The listing applies to risperidone 500 microgram and 1 mg scored tablets, 500 microgram and 1 mg orally disintegrating tablets (Quicklet) and oral solution 1 mg per mL, 30 mL.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended listing on the basis of acceptable cost-effectiveness compared to haloperidol. Risperidone was considered to have a lower propensity for tardive dyskinesia than haloperidol.[1,2]

Place in therapy

Drug treatment has uncertain benefits and may cause serious adverse effects so is second-line treatment for behavioural disturbances in dementia. Managing underlying causes and non-drug strategies should be tried first.

Identifying and, where possible, modifying triggers for problem behaviours may help to avoid the need for drug therapy. Consider whether physical illness, depression, anxiety, the environment or interactions with others are contributing to behavioural disturbances.

It is difficult to recommend any non-drug strategy above another on the basis of current evidence. However, combinations of interventions tailored to the needs of individuals and carers may improve both patient behaviour and carer distress.[3,4]

Risperidone produces modest improvements in problem behaviours characterised by psychosis and aggression. There is no conclusive evidence that it is any more effective than other drugs, but it is the only atypical antipsychotic that is both approved by the Therapeutic Goods Administration **and** PBS-listed for this indication.

Encourage carers and people with dementia to seek support and provide them with information about available services. The National Dementia Behaviour Advisory Service (ph. 1300 366 448) provides information to health professionals and carers about dealing with problem behaviours.

Safety issues

Elderly patients are more susceptible than younger patients to the adverse effects of risperidone. Extrapyramidal side-effects, postural hypotension and somnolence are dose-related.[5] Consider each patient's risk of cerebrovascular adverse events and diabetes mellitus; risperidone may increase the risk of both.

Dosing issues

Starting doses and target doses should be lower and dose titration slower in the elderly than in younger patients. Consider ceasing or reducing the dose if adverse effects occur.

Regularly review the need for continuing therapy with a view to reducing the dose or ceasing. Behavioural disturbances may be short-lived, so drug therapy should not be prescribed indefinitely.

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See the full *NPS RADAR* review of risperidone at www.npsradar.org.au for a discussion of the evidence for risperidone's efficacy in behavioural disturbances in dementia, the potential risk of cerebrovascular events, hyperglycaemia and extrapyramidal adverse effects, and information and support services for carers of people with dementia.

Patient support organisation

Alzheimer's Australia

Alzheimer's Australia provides a range of sensitive and flexible services to support people with any type of dementia, their families and carers throughout the illness. These services include information about dementia, a 24-hour Dementia Helpline, an Interpreter Service, support groups for people who have been diagnosed with dementia, private and confidential counselling, and other local programs. Services differ slightly between the state organisations. The website of Alzheimer's Australia contains useful 'Help sheets for family and carers' on such topics as communication, driving, going to hospital, wandering, pain, safety issues, etc.

Contact information

24-hour Dementia Helpline	1800 639 331
Website	www.alzheimers.org.au
Interpreter Service	131 450
National Dementia Behaviour Advisory Service (for carers concerned about the behaviours of people with dementia)	1300 366 448

Australian Capital Territory
Alzheimer's Australia ACT
Frewin Place
SCULLIN ACT 2614
Phone: (02) 6254 5544
Fax: (02) 6254 2522
Email: admin@alzheimersact.asn.au

New South Wales
Alzheimer's Australia NSW
Macquarie Hospital Campus
Cox's Road Entrance
NORTH RYDE NSW 2113
Phone: (02) 9805 0100
Fax: (02) 9805 1665
Email: admin@alznsw.asn.au

Northern Territory
Alzheimer's Australia NT Inc.
Darwin
Nightcliff Community Centre
Suite 3/18 Bauhinia Street
NIGHTCLIFF NT 0814
Phone: (08) 8948 5228
Fax: (08) 8948 5229
Email: admin@alzheimersnt.org.au

Alice Springs
Shop 5 Cinema Complex Breezeway
Todd Mall
ALICE SPRINGS NT 0870
Phone: (08) 8952 9799
Fax: (08) 8952 9796

Queensland
Alzheimer's Australia (Queensland) Inc.
90 Allied Drive
ARUNDEL QLD 4214
Phone: (07) 5574 6224
Fax: (07) 5571 5987
Email: info@alzqld.asn.au
Regional offices: Darling Downs and South West, Gold Coast, North Queensland, Sunshine Coast (Dementia), Central Queensland

South Australia
Alzheimer's Australia SA Inc.
27 Conyngham Street
GLENSIDE SA 5065
Phone: (08) 8372 2100
Fax: (08) 8338 3390
Email: alzsa@alzheimerssa.asn.au

Tasmania
Dementia and Alzheimer's Association (Tasmania) Inc.
The Old Vicarage
St John's Avenue
NEW TOWN TAS 7008
Phone: (03) 6278 9897
Fax: (03) 6278 9878
Email: debbie.slater@alztas.asn.au

Victoria
Alzheimer's Australia Vic.
98–104 Riversdale Road
HAWTHORN VIC 3122
Phone: (03) 9815 7800
Fax: (03) 9815 7801
Email: alz@alzvic.asn.au

Western Australia
Alzheimer's Australia WA
Mary Chester Centre
9 Bedbrook Place
SHENTON PARK WA 6008
Phone: (08) 9388 2800
Fax: (08) 9388 2739
Email: alzwa@alzheimers.asn.au
Website: www.alzheimers.asn.au
Regional offices: York, Albany, Kalgoorlie, Mandurah, Rockingham, Bunbury

What's new in smoking cessation?

John Litt, Senior Lecturer in General Practice, School of Medicine, Flinders University, Adelaide

Summary

Tobacco smoking is the main preventable cause of morbidity and mortality in Australia. Recently published evidence-based guidelines for general practitioners recommend the 5As framework which is consistent with other international guidelines. Active follow-up of smokers by Quitline and the use of nurses to provide smoking cessation activities are two interventions that are likely to expand the reach of smoking cessation services and increase their effectiveness. Combination pharmacotherapies for nicotine dependence should be considered in smokers who have had difficulty quitting despite the concurrent use of brief behavioural counselling and pharmacotherapy.

Key words: nicotine, patient support.

(Aust Prescr 2005;28:73–5)

Introduction

Every year in Australia, tobacco smoking causes an estimated 19 000 deaths and up to 10% of hospital separations in people aged 35 years and over.[1] The 50-year follow-up of the British doctors study shows that up to 66% of lifelong smokers are likely to die from a tobacco-related disease with half these deaths occurring prematurely.[2] No other single avoidable factor accounts for such a high proportion of deaths.[1]

Health professionals have several strategies they can use to encourage patients to quit smoking. In addition to the publication of the first Australian smoking cessation guidelines for general practice in 2004[1], there have been a number of other developments. These include:

- increasing evidence for the effectiveness of:
  - active callback programs by the Quitline[3,4]
  - nurses providing smoking cessation in the primary care setting[5]
- the need to consider the use of combination pharmacotherapies in assisting smokers to quit.[6]

Smoking cessation guidelines for Australian general practice

The Australian general practice guidelines for smoking cessation follow the 5As framework (Table 1). To assist busy practitioners in summarising the effective smoking cessation activities a time-tiered synopsis of the 5As approach has also been published.* This intervention can be delivered in one minute or less.[7]

Active callback programs by telephone quit lines

Several recent randomised controlled trials in Australia and the USA have found an advantage in offering telephone follow-up to smokers referred to a quit line. Active follow-up (4–5 calls on average) in the first three months of quitting is associated with higher 12-month quit rates (between 22%[3] and 25.8%[4]) than more passive referrals to the Quitline. This represents four more people quitting for every 100 counselled.

Nurse-delivered smoking cessation strategies

A systematic review has found that nurses have a similar impact to doctors when providing smoking cessation in primary care.[5] The main findings of the systematic review were:

- smokers offered advice by a nurse had an increased likelihood of quitting compared to smokers without nursing intervention (3–4 extra quitters for each 100 counselled)
- smoking intervention in the 13 trials involving non-hospitalised adults gave an approximately 80% increase in the odds of success
- there was no evidence from indirect comparisons that higher intensity interventions were more effective in achieving successful quitting.

Overall, the results revealed that brief smoking cessation interventions provided by nurses significantly increase the odds of quitting compared to usual care.

Combination pharmacotherapies in assisting smokers to quit

With the slow fall in the prevalence of smoking, the current population of smokers represent a mix of 'hardened' smokers who have attempted to quit on a number of occasions and others, for example younger smokers.[8] Both groups are exposed to increasing community awareness of the harmful effects of smoking and expanding legislative changes to quit.

* A summary copy of the time-tiered 5As approach to smoking cessation can be found on the Cancer Council SA website http://www.cancersa.org.au/i-cms_file?page=544/GPdeskprompt.pdf [cited 2005 May 10]

Table 1

5As smoking cessation framework *

5As	Strategy	Suggested approach
Ask	Identify and document smoking status at least every 12 months	Hand out brief patient survey in the waiting room to identify smoking status
Assess	Interest in quitting	How do you feel about your smoking at the moment? How would you rate your interest in quitting right now on a scale of 1–10 where 10 equals very interested in quitting? What do you like and dislike about smoking?
	Barriers to quitting	What would be the hardest thing about quitting?
	Level of nicotine dependence	Time to first cigarette from waking (less than 30 minutes) Smokes 15 or more cigarettes a day Evidence of withdrawal symptoms with previous quit attempts
	Quitting history	What has worked before? What hasn't worked?
	High risk situations	What would be the hardest cigarette to give up?
Advise	Provide clear, brief and non-judgemental advice to quit	As your doctor, I strongly suggest that you stop smoking Quitting is the most important thing you can do to stay healthy
	Address the three domains	Nicotine dependence Habit Psychological aspects of smoking
Assist	Quit services	Refer to Quitline 131 848 † Offer Quit book Enrol in Quitline callback program
	Pharmacotherapy	Discuss pharmacotherapy e.g. nicotine replacement therapies and bupropion
	Address barriers to quitting	Commonly: – stress – weight gain – negative emotions – lack of support – fear of failure – low self-confidence
Arrange	Follow-up	Review pharmacotherapy Advise about relapse prevention Review progress
	Support	Offer your support Enlist support of significant others

* adapted from 'Smoking cessation guidelines for Australian general practice'[1], GPs Assisting Smokers Program (GASP)[7] and 'Treatment of tobacco use and dependence'[9]

† in all states except Queensland

Identification of readiness to change, level of nicotine dependence and number of previous quit attempts will assist the practitioner in the approach to cessation, especially the use of pharmacotherapy.

Like other pharmacological treatments, combination therapy using drugs with different modes of action has been tried with differing degrees of success.[6] Combination therapy can include two alternative forms of nicotine replacement therapy (NRT) or nicotine replacement and buproprion when 'the smoker has not been successful on an adequate trial of one of these therapies'.[1] Most formulations of NRT provide doses of nicotine that are below that achieved by smoking.[1] Combination NRT includes a formulation that provides basal levels of nicotine (for example nicotine patch) with 'top up' doses when withdrawal and craving

are more likely to be a problem, for example first thing in the morning. Top up doses can be provided by a nicotine inhaler, lozenge or gum. Combination therapies should be considered in smokers who have failed despite behavioural intervention and a reasonable trial of a single formulation.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

7. Telephone follow-up by a quit line service increases the chance of a smoker successfully quitting smoking.
8. Patients should not use two forms of nicotine replacement therapy at the same time.

New drugs

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

Bivalirudin

Angiomax (CSL)

vials containing 250 mg lyophilised powder for reconstitution

Approved indication: percutaneous coronary intervention

Australian Medicines Handbook section 7.1

Patients having procedures such as percutaneous transluminal coronary angioplasty need to be anticoagulated. While heparin can be used, some patients still develop ischaemia and there is a risk of major bleeding.

Bivalirudin is a direct inhibitor of thrombin related to the anticoagulant protein produced by leeches. By reversibly binding to thrombin, bivalirudin stops the conversion of fibrinogen to fibrin and inhibits platelet aggregation.

The anticoagulant effect begins within a few minutes of intravenous administration. The clotting time, activated partial thromboplastin time (APTT), prothrombin time and thrombin time are all increased. Bivalirudin is given as a bolus dose followed by an infusion. It has a half-life of approximately 25 minutes, with most of the dose being metabolised into amino acids. As 20% of the dose is excreted unchanged in the urine impaired renal function prolongs the half-life.

An early study of bivalirudin found that it caused less bleeding but had no greater efficacy than high-dose heparin in preventing ischaemic complications in patients having coronary angioplasty.[1] Development of the drug did not proceed, however when the results were reanalysed several years later they showed a statistical advantage for bivalirudin.[2] As the drugs used during the procedure had changed in the intervening years, there was a need to evaluate bivalirudin with the new approaches.

The REPLACE-2 trial randomised 6010 patients to receive bivalirudin or heparin plus a glycoprotein IIb/IIIa inhibitor. All patients also received aspirin and the use of clopidogrel was

encouraged. Analysis at 30 days revealed that 7.6% of the bivalirudin group had died, had an infarction or needed urgent revascularisation. In the heparin/glycoprotein inhibitor group 7.1% of the patients reached the same end point. While the two approaches had similar efficacy, bivalirudin significantly reduced major bleeding. Major bleeding occurred in 4.1% of the patients given heparin and a glycoprotein inhibitor compared with 2.5% of the bivalirudin group.[3]

The patients in REPLACE-2 were followed up for a year. After six months there were fewer deaths in the bivalirudin group, but more myocardial infarctions and revascularisations. Although the mortality with bivalirudin was lower after 12 months it was not significantly different from the mortality with heparin.[4]

In addition to bleeding, patients may develop back pain. Unlike heparin, bivalirudin does not cause an immune thrombocytopenia, but it has been associated with thrombocytopenia.

Although bivalirudin causes less bleeding than heparin and a glycoprotein inhibitor, its role in therapy probably requires further study. The higher cost of bivalirudin will also need to be considered before it can replace heparin in general use.

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Cinacalcet hydrochloride

Sensipar (Amgen)

30 mg, 60 mg and 90 mg tablets

Approved indications: hyperparathyroidism, hypercalcaemia

Australian Medicines Handbook section 10.3

Parathyroid hormone increases calcium concentrations by increasing bone resorption and the reabsorption of calcium by the kidney. Adenomas of the parathyroid glands cause primary hyperparathyroidism and parathyroidectomy may be indicated. Secondary hyperparathyroidism is a reaction to hypocalcaemia which can have a variety of causes such as renal failure or vitamin D deficiency.

The secretion of parathyroid hormone depends on a receptor which senses the serum calcium concentration. By increasing the sensitivity of this receptor to calcium, treatment with cinacalcet reduces the secretion of parathyroid hormone which in turn reduces the calcium concentration.

Cinacalcet tablets have a bioavailability of 20–25%, but this increases if they are taken with food. Peak plasma concentrations are achieved 2–6 hours after a dose and this corresponds with the nadir of parathyroid hormone secretion. This suppression lasts long enough to allow once-daily dosing for secondary hyperparathyroidism. Cinacalcet is cleared by metabolism which includes cytochrome P450 3A4, 2D6 and 1A2. This results in interactions with drugs such as ketoconazole and rifampicin. Smoking increases clearance by inducing P450 1A2.

Several small studies have investigated cinacalcet in patients with primary hyperparathyroidism or parathyroid carcinoma. A short dose-ranging study found that cinacalcet significantly decreased the serum calcium concentration. In one study, a twice-daily dose of 30 mg reduced the concentration by 11% and 50 mg twice daily reduced it by 18.5%. At its nadir the concentration of parathyroid hormone fell by half.[1] Doses should be titrated according to the hormone or calcium concentration.

More data are available on the use of cinacalcet to treat secondary hyperparathyroidism in patients having renal dialysis. In a 26-week study, 741 patients were randomised to receive once-daily cinacalcet or placebo. Mean concentrations of parathyroid hormone were reduced by 43% in the cinacalcet group, but increased by 9% in the placebo group. However, only 43% of the patients taking cinacalcet reached the target concentration of parathyroid hormone.[2]

Nausea and vomiting are the most frequent adverse reactions to cinacalcet. Less common adverse events are hypocalcaemia, convulsions and paraesthesia.

The studies of cinacalcet have focussed on biochemical tests. There is little information on clinically important outcomes, particularly in primary hyperparathyroidism. Although cinacalcet may be useful in treating the hypercalcaemia associated with parathyroid carcinoma, its approval in primary hyperparathyroidism is restricted to patients who cannot have a parathyroidectomy. While cinacalcet is efficacious in reducing parathyroid hormone concentrations in secondary hyperparathyroidism in patients having renal dialysis, longer-term studies will be needed to assess its effect on bone and the vascular system.

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Everolimus

Certican (Novartis)

0.25 mg, 0.5 mg and 0.75 mg tablets

Approved indication: transplantation

Australian Medicines Handbook section 14.1

Everolimus is a derivative of the immunosuppressant drug sirolimus. It has been approved for use by patients receiving a heart or kidney transplant.

Although patients' survival after transplant has improved, problems may develop in the long term. For example, treatment with cyclosporin can damage the transplanted kidney and vasculopathy may complicate heart transplants. Everolimus may therefore have a role in preventing organ rejection because it inhibits cell proliferation. This inhibition includes vascular smooth muscle cells as well as T-cells.

Treatment begins as soon as possible after transplantation. Peak concentrations occur within two hours of an oral dose, but absorption is reduced by food. Steady state concentrations are reached within four days. Everolimus is metabolised by liver enzymes including cytochrome P450 3A4. Most of the metabolites are excreted in the faeces. The half-life of everolimus is approximately 28 hours.

Everolimus was compared with azathioprine in patients following heart transplantation. These 634 patients were also treated with cyclosporin, corticosteroids and a 'statin'. The end point of the study was a mixture of death or rejection. After 12 months, 52.8% of the azathioprine group had reached this end point. This was significantly more than the 41.6% of the 209 patients given everolimus 1.5 mg, and the 32.2% of the 211 patients given everolimus 3.0 mg.[1]

Studies in renal transplantation used mycofenolate mofetil as a comparator. Rejection had occurred by six months in 23.5% of the mycofenolate group, 21.6% of those taking everolimus 1.5 mg and 18.2% of those taking everolimus 3.0 mg.

Two studies used everolimus to lower the dose of cyclosporin used after renal transplantation. Although there was no comparator arm in the studies, both doses of everolimus were associated with satisfactory renal function after six months.[2]

As rejection occurs more frequently with lower concentrations, the blood concentration of everolimus must be monitored regularly. More frequent monitoring will be needed if the patient is started on a drug which inhibits (ketoconazole) or induces (rifampicin) CYP3A4.

Adverse events occur in almost everyone treated with everolimus. Approximately 10–22% of patients will discontinue treatment because of adverse events. These include anaemia, leucopenia, thrombocytopenia and infections.[1,2] In the heart transplant study significantly more bacterial infections occurred in the everolimus group. Even if the patients are taking 'statins' their triglyceride and cholesterol concentrations are likely to increase.[1]

Managing patients after transplantation requires balancing the risk of organ rejection against the adverse effects of immunosuppression. Further study will be needed to define the place of everolimus. The results of a Cochrane review of the effects of everolimus and sirolimus in renal transplantation are not yet available.[3]

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Poractant alfa

Curosurf (Douglas)

vials containing 120 mg/1.5 mL and 240 mg/3 mL

Approved indication: neonatal respiratory distress syndrome

Australian Medicines Handbook section 19.6.2

Surfactant lowers the surface tension of the alveolar membrane. Premature infants lack surfactant so their alveoli can collapse leading to respiratory distress. The respiratory distress syndrome can be managed or prevented by administering a substitute surfactant down an endotracheal tube. The first artificial surfactant was colfosceril palmitate, but this is no longer marketed in Australia. Beractant is still available. It is a surfactant derived from cows' lungs, whereas poractant alfa is derived from pigs' lungs.

Most of the early trials of poractant alfa were in Europe where it has been approved for marketing for more than 10 years. In a study of 146 babies with respiratory distress syndrome the 28-day mortality rate was 31% in the group who received poractant compared with 51% in the group who did not.[1] Two years later there were no differences between the groups in growth, disability and respiratory symptoms.[2]

If the baby does not respond to the first dose, a half dose may be given after 12 and after 24 hours. Babies given repeat doses have a lower mortality rate at 28 days than those given a single dose (13% versus 21%).[3]

Subsequent studies have investigated if giving poractant to babies at risk of respiratory distress is more effective than waiting for the syndrome to appear. A meta-analysis of these studies showed that the neonatal mortality rate was 15% when poractant was used for prophylaxis and 25% when it was used for treatment. However, prophylaxis did not have a significant advantage in the prevention of chronic lung disease of the newborn.[4]

Administering poractant is not without risk. The endotracheal tube can get blocked and the baby may develop oxygen desaturation, hypotension and bradycardia.

Clinicians now have a choice of using beractant or poractant. Comparative trials suggest that poractant improves oxygenation more rapidly.[5,6]

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Pregabalin

Lyrica (Pfizer)

75 mg, 150 mg and 300 mg capsules

Approved indications: epilepsy, neuropathic pain

Australian Medicines Handbook section 16.1

Gamma-aminobutyric acid (GABA) is a neurotransmitter. Although pregabalin is an analogue of GABA, its therapeutic effect may be on other neural pathways. Pregabalin reduces the release of neurotransmitters by interfering with the calcium channels in nerve terminals. It has therefore been studied in neuropathic pain and as an adjunctive treatment for epilepsy.

Common examples of neuropathic pain are diabetic neuropathy and post-herpetic neuralgia. In a double-blind trial involving 146 patients with diabetic neuropathy pregabalin was more efficacious than placebo at reducing pain. After eight weeks of treatment the pain of the patients taking pregabalin had reduced by 2.5 points, on an 11 point scale, compared with a 0.8 decrease in the placebo group.[1] In another eight-week double-blind trial, which included some Australian patients, pregabalin reduced the pain of herpetic neuralgia more than placebo did. Compared to placebo, mean pain scores were 1.2 points lower with pregabalin 150 mg/day and 1.57 points lower with 300 mg/day.[2]

Most patients with epilepsy can be managed with monotherapy, but some will need adjunctive treatment. Pregabalin has been studied as adjunctive treatment for patients with partial seizures, with or without secondary generalised seizures. An international study compared adding pregabalin with adding placebo to the treatment of 287 patients. After 12 weeks there was no decrease in seizure frequency in the placebo group, but a 20.6% reduction in the pregabalin 150 mg/day group and a 47.8% reduction in the 600 mg/day group. Approximately 44% of the patients taking the higher dose of pregabalin had at least a 50% reduction in seizure frequency.[3]

As pregabalin alters neurotransmission it can cause a variety of neurological adverse effects. In the neuropathic pain studies 28–36% of the patients taking 300 mg/day developed dizziness and 20–24% developed somnolence.[1,2] Other common problems include ataxia, co-ordination problems, confusion and altered vision. Patients are therefore advised not to drive, until the effects of pregabalin are known. Other complaints include peripheral oedema, weight gain and dry mouth.

Most of a dose of pregabalin is excreted unchanged in the urine, with an elimination half-life of six hours. Lower doses are required if the patient has a reduced creatinine clearance.

While pregabalin has met the efficacy criteria for pain relief it is important to note that the response varies between patients. Only 32% of the patients with post-herpetic neuralgia will feel much improved, or very much improved with treatment. The response tends to be greater in patients with somnolence.

There is also a variation in the response of patients with epilepsy. Although seizure frequency will be at least halved in approximately 44% of patients given 600 mg/day, the responder rate with 150 mg/day is not significantly different from placebo (14% versus 6.2%). While 150 mg/day is an acceptable starting dose it may need to be gradually increased.[3]

Chronic pain and epilepsy are long-term problems so there need to be long-term studies of pregabalin to see if its benefits are maintained in the people who respond, and to see if any other adverse effects emerge . There is also a need to see how pregabalin compares with drugs, such as gabapentin, which have similar indications.

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

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

NEW FORMULATIONS

Hydromorphone hydrochloride

Palladone XL (Mundipharma)

12 mg, 16 mg, 24 mg and 32 mg extended release capsules

Timolol maleate

Nyogel (Novartis)

1.37 mg/g eye gel

NEW BRAND

Irinotecan hydrochloride

Irinotecan (Mayne Pharma)

vials containing 40 mg/2 mL and 100 mg/5 mL for injection

Correction

Ketotifen hydrogen fumarate (Aust Prescr 2005;28:19–23)

The recommended Australian dosage is one drop twice daily.

Answers to self-test questions

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

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

Typesetting
Barnes Desktopping and Design

Printed in Australia by
National Capital Printing
22 Pirie Street, Fyshwick, ACT 2609

Published by the
National Prescribing Service Ltd, an independent, non-profit organisation funded by the Australian Department of Health and Ageing

NPS
National Prescribing Service Limited

INTERNATIONAL SOCIETY OF DRUG BULLETINS

Print Post Approved PP349181/00151 • ISSN 0312-8008