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CONTENTS

Editorial

Pharmaceutical Benefits Scheme cost recovery

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Key words: cost-effectiveness, drug industry.

(Aust Prescr 2011;34:62–3)

Since the beginning of 2010 the Australian Government has applied cost recovery to the listing process of the Pharmaceutical Benefits Scheme (PBS). Drug companies seeking to list their drugs on the PBS or vaccines on the National Immunisation Program pay a fee at two key points – upon lodgement of the application and at the pricing stage.[1] The lodgement fee relates to the evaluation work of the Pharmaceutical Benefits Advisory Committee (PBAC) and all of its supporting administrative functions. The pricing fee relates to the pricing work of the Pharmaceutical Benefits Pricing Authority and its supporting functions. Companies that want an independent review of a PBAC recommendation to not list a drug on the PBS will also pay. The fees are not trivial – $119 500 for a major PBAC evaluation, $25 000 for a complex 'pricing' and $119 500 for an independent review.[2] Hardly spare change, even for a pharmaceutical company. So what is the purpose of the cost recovery scheme and what are the likely consequences?

In this issue…

The cost of the Pharmaceutical Benefits Scheme will always be a topic for debate, but it is important to know that the evaluations of cost-effectiveness are assessed by the independent Pharmaceutical Benefits Advisory Committee. Glenn Salkeld reassures us that the introduction of evaluation fees will not compromise this independence.

Independence is also important when assessing information about medicines. Rosalind Tindale tells us where to find independent sources of drug information.

Genetic information has changed the way haemochromatosis is investigated. Andrew St John, Katherine Stuart and Darrell Crawford review how to make the diagnosis.

The prognosis for patients with HIV has improved, but regular monitoring and adherence to treatment are essential. Tom Turnbull provides advice on how general practitioners can assist in management.

The management of sleep apnoea may also involve a range of health professionals. Stuart MacKay outlines some of the treatment options.

The stated purpose is to recover the cost of the services provided (evaluation and pricing) and to promote efficient allocation of resources.[1] Depending on your point of view it is either an attempt to gouge the pockets of industry or a 'fair cop guv'. After all, the pharmaceutical industry does very nicely from PBS price subsidies, and so does the Australian public. All parties benefit from the PBS – the key question is whether cost recovery threatens the very process that has delivered safe, timely and affordable access to prescribed medicines for all Australians.

Some of the early response to the cost recovery proposal has been reminiscent of the reaction when the PBAC started to assess the cost-effectiveness of drugs (National Health Amendment Bill 1987). It was feared that the extra cost of preparing submissions would result in Australia missing out on new drugs. However, the PBAC cost-effectiveness process is designed to reward sponsors with higher prices for drugs that provide greater clinical benefit than the drugs which are currently available. It does not reward those drugs that do not confer additional clinical benefit. Without the cost-effectiveness requirement the PBS would probably have sunk under the weight of its own success. It may still do so unless pharmaceutical expenditure is kept under tight control. There are, however, legitimate concerns about cost recovery.

The first concern is that PBS cost recovery may be the straw that will break the camel's back. The pharmaceutical industry is already carrying the load of lower profits, fewer blockbuster drugs in the pipeline and the high cost of getting a drug to market. Critics of cost recovery argue that some new drugs may never enter the Australian market due to higher costs of registration and PBS listing (or face lengthy delays in reaching our shores). Those that do will be more expensive (as companies will pass on the extra cost of PBS listing) and smaller companies may be driven out of the market. Furthermore, cost recovery may discourage development of drugs aimed at a lower volume market.

Let us get some perspective here. In 2008–09, the Australian Government spent more than $7.679 billion on pharmaceutical benefits.[3] That is taxpayer dollars that not only provide health benefits to millions of Australians but also contribute directly to bottom line industry profits. At face value industry can afford the extra impost of cost recovery. It is unlikely that new drugs

will be prevented or delayed in reaching the Australian market. The Australian pharmaceutical market is a competitive one and 'if a company decides not to launch a particular product in Australia, then competitors' products come in'.[4] If there is no competitor then it is possible that a sole manufacturer may decide not to introduce a new product to the Australian market. It is a commercial decision. If cost recovery fees alone swing the manufacturer's net present value calculation of a new drug from a decision to submit (to the Therapeutic Goods Administration (TGA) and subsequently to PBAC) to 'not submit', then the case for registration and PBS listing is likely to have been marginal in the first place.

Another concern is that cost recovery may compromise the independence of the PBAC, because it will be paid by the drug companies. This fear appears to be unfounded because the PBAC has no direct pecuniary interest in the process. All the income from cost recovery fees goes into consolidated revenue rather than to the PBAC itself. Neither the Department of Health and Ageing nor the PBAC would actually see any of the 'cost recovery' funds. Historically the PBAC has shown itself to be strongly independent. Since 1998–99 the TGA has operated on a full cost recovery basis. I have not seen evidence to suggest that the TGA has been compromised by the introduction of cost recovery.

It is fair to say that a lot of effort has gone into making the PBAC process more transparent and responsive to the needs of drug companies and this preceded the introduction of cost recovery. The industry's expectations of the process may increase as a result of the new fees, with an understandable desire for quicker turnaround of PBAC submissions. Time will tell how the PBAC responds to the concurrent demands of meeting their legislative requirements and managing what is the inherently adversarial nature of negotiating drug prices.

Of course there are instances when the imposition of the cost recovery fee is not in the public interest. Under the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009[2] an exemption may be granted in respect of orphan drugs, the temporary supply of drugs or changes to an existing PBS listing. A fee waiver may be granted if 'the application involves the public interest and payment of the fee would make the application financially unviable'. This may apply when the patient population is not large enough to make the application financially viable, the product is to be used for palliative care or as a paediatric medicine, or for treatment of Aboriginal or Torres Strait Islander people.

For any change in policy it pays to be vigilant and monitor any unintended consequences. If experience is anything to go by, the PBAC process will survive. Numerous reviews and a few detractors have not weakened the inherent strength of a legislated process that supports evidence-based decision making.

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Professor Salkeld has received an honorarium from Pfizer for teaching a short course on 'cost-effectiveness of pharmaceuticals'.

Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

Denosumab

Editor, – We welcome being recognised for transparency in supplying Therapeutic Goods Administration (TGA) evaluation data to *Australian Prescriber* to assist in the preparation of the new drug comment about denosumab (Prolia) (Aust Prescr 2010;33:194).

We were, however, surprised to read a statement, based on a meta-analysis[1] that 'denosumab was not associated with a significant reduction in fracture risk in postmenopausal women', despite your review having previously described a clinical trial which showed statistically significant reductions

in the incidence of vertebral, non-vertebral and hip fracture. This trial recruited 7868 patients and fractures were an independently adjudicated endpoint.[2]

The meta-analysis included three studies (996 patients in total) including a dose-ranging phase 2 study and a study in women with bone loss related to hormone ablative therapy for breast cancer (not an approved indication). Fractures were not a pre-planned outcome in any study analysed and were collected only as adverse events, neither confirmed nor independently adjudicated. Following the peer-reviewed publication of the pivotal fracture trial,[2] any reference to the meta-analysis is profoundly limited.

The omission of these limitations from the new drug comment could leave the reader with the impression that the meta-analysis included data from the trial[2] and that the statistically significant fracture outcomes were negated by the other studies in the meta-analysis.

We feel it important to highlight this so as not to mislead prescribers into believing that the TGA have granted marketing authorisation for a product that is '... not associated with a significant reduction in fracture risk in postmenopausal women'.

Cae Tolman
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Arterial blood gases

Editor, – I read with concern the article on arterial blood gases (Aust Prescr 2010;33:124-9). I believe the emphasis of arterial blood gases over venous blood gases is no longer representative of what is being taught and practised in acute care medicine.

Venous blood gases are easier to obtain, hurt less, are safer and provide extra information about tissue oxygen use that arterial blood gases do not. In combination with a pulse oximeter reading, venous blood gases can be used to guide clinical decision making in the majority of situations where arterial blood gases have previously been thought to be necessary. Venous blood gases are therefore better than arterial blood gases most of the time.

Arterial blood gases are now rarely obtained from patients in emergency departments, especially children, unless there is repeated sampling from an arterial line, usually inserted for haemodynamic monitoring. This is because venous blood gases (along with pulse oximetry) provide adequate information for the majority of acute paediatric and adult clinical scenarios, including sepsis, asthma, chronic lung disease, toxicology, diabetic ketoacidosis, and therapy adjustments for invasive and non-invasive ventilation. Reviews in the literature aim to educate that venous blood gases can replace arterial blood gases in most acute care clinical scenarios.[1,2]

Decisions involving oxygenation can be made with information from a pulse oximeter, unless there is poor waveform. Modern pulse oximeters are accurate +/– 2% down to saturations as low as 70%. Given this accuracy, it is questionable concerning the value of arterial verses venous blood gases and pulse oximetry to assess the need for domiciliary oxygen therapy.

Although local anaesthetic reduces the pain of arterial blood gases sampling without decreasing success rates, a better option is to just not do them at all.

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Ringwood East, Vic.

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Dr Abhishek Verma and Dr Paul Roach, authors of the article, comment:

We acknowledge that in the acute setting, sampling venous blood is sufficient to obtain information about a patient's acid–base and ventilation status. Combined with pulse oximetry, venous blood gases are useful in a variety of clinical scenarios. However, there are some important caveats. It is essential to obtain a good waveform for pulse oximetry if the result is used for estimating the oxygen saturation and partial pressure. Yet, in several acute situations – for instance, sepsis, trauma or cardiac arrest – peripheral circulation may be inadequate so it is difficult to obtain any information about potential hypoxaemia. Pulse oximetry can also be influenced by other factors, such as if the patient is vasoconstricted due to inotrope use or is excessively moving or shivering. Also when a patient presents with toxic gas exposure or carbon monoxide

poisoning, a falsely high oximetry reading may confound the recognition of severe tissue hypoxaemia. Taking an arterial blood gas sample in these instances ameliorates the problems of estimating the oxygenation entirely.

Pulse oximetry, while being a far less invasive method of determining the state of oxygenation than arterial blood gas analysis, does rely on an understanding of the physiology of the oxygen–haemoglobin disassociation curve. These are concepts that many medical students and junior doctors are not always cognisant of, and so the interpretation of oxygenation status from an arterial blood gas sample remains important.

Current Australian guidelines still require arterial blood gas analysis before domiciliary oxygen can be legally prescribed. Accordingly, the performance and interpretation of arterial blood gases remains a very important skill for a clinician.

Management of delirium in the elderly

Editor, – Thank you to Dr Caplan for the excellent and timely review of the management of delirium in the elderly (Aust Prescr 2011;34:16-8). Benzodiazepines (diazepam in particular) are the treatment of choice for delirium tremens in Australia. I would like to point out that benzodiazepines can at times be the cause of delirium.

Midazolam, diazepam, triazolam, lorazepam and clonazepam have all been reported to cause confusion, agitation, aggression and disinhibition in the very young and elderly. This is the so-called 'paradoxical reaction' from benzodiazepines.

Paradoxical reaction has been reported as a rare condition in the normal population. However, past reports suggest that its incidence is significant in certain populations such as intensive care patients and postoperative elderly patients, particularly elderly people with risk factors for delirium, as pointed out by Dr Caplan.

I have encountered a number of elderly patients given diazepam for alcohol withdrawal who have developed confusion, agitation and on rare occasions hallucination. The most severe cases are those managed by inexperienced resident medical officers who have mistaken the presentations with delirium tremens. The patients were given cumulatively large doses of diazepam as a result and their condition deteriorated further. It is a reminder to us all that the elderly can be more at risk of adverse reactions to medications, and often conservative measures as listed by Dr Caplan should be the treatment of choice.

Raymond Chan
Addiction medicine physician
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Dr G Caplan, author of the article, comments:

I thank Dr Chan for his kind words. There is no doubt that cumulatively large doses of benzodiazepines, as well as antipsychotics, will frequently exacerbate delirium in older patients. Dosing schedules for young patients with psychosis or delirium may act as a recipe for disaster in older patients. There is also evidence from a small randomised controlled trial in young AIDS patients that lorazepam is not an effective treatment for delirium and perhaps makes things worse. However the comparators, haloperidol and chlorpromazine, were effective,[1] as antipsychotics have been in other trials.

Because of the hazards of drug interactions and adverse effects, initial management should always focus on stopping drugs that may be aetiological.

Reference

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Therapeutic Guidelines: Oral and Dental

Editor, – Associate Professor Michael McCullough says that Therapeutic Guidelines: Oral and Dental is now available to every member of the Australian Dental Association and dental students (Aust Prescr 2010;33:167-70). Does this also apply to the foreign trained dentists who are now practising in Australia? Many of them are working in rural and remote areas with very little peer support and do not appear to be receiving education on accepted Australian therapeutic practices.

As a pharmacist involved in remote and rural and indigenous health issues, I have had many discussions with dentists who have been trained in different treatment protocols from what is accepted as best therapeutic practice in Australia. What is the Australian Dental Association doing to assist this growing number of foreign trained dentists? The professional isolation for these practitioners is of concern to both them and the pharmacists who dispense their prescriptions.

Karalyn J Huxhagen
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Associate Professor Michael McCullough comments:

The Australian Dental Association supplies the Therapeutic Guidelines: Oral and Dental to its members for free. Overseas trained dentists are strongly encouraged to join the Australian Dental Association and are treated as student members

before they are registered with the Dental Board of Australia. Overseas trained dentists must pass the Australian Dental Council exams before registration and there is a strong expectation that candidates for these exams will have thorough knowledge of the accepted best therapeutic practice for dentistry as outlined in Therapeutic Guidelines. Without full knowledge of these guidelines it would be extremely unlikely that candidates would pass these very difficult exams.

The Australian Dental Association is very concerned about all rural and remote practising dentists and in particular those trained overseas. It runs an excellent professional development program targeting remote dentists. The program is delivered via the internet as 'webinars' which are generally held in the early evening to have least disturbance to clinical practice. The most recent webinars were extremely well attended (over 70 participants). This service is free and all dentists, particularly overseas trained dentists working in remote regions of Australia where professional interaction is more difficult, should be encouraged to join the Australian Dental Association and access these services.

Book reviews

Nursing Spectrum Drug Handbook

Schull PD. New York: McGraw-Hill; 2010. 1376 pages. $48.

Nurse's Pocket Drug Guide

Barberio JA. New York: McGraw-Hill; 2010. 409 pages. $20.

***Di Crellin**, Nurse practitioner, Royal Children's Hospital, Melbourne, and Lecturer, University of Melbourne*

These books aim to provide comprehensive detail for nurses about a wide range of medications to ensure safe prescription and administration. They contain a lot of information, but it has a North American focus.

The Handbook has comprehensive details, and as a resource intended for nurses the included sections titled 'Administration', 'Patient monitoring' and 'Patient education' focus heavily on the nursing responsibilities of medication management and are a strength of the text.

The content has a section on 'Safe drug administration', which includes a range of useful resources, the majority of which will serve as a quick reference guide before administering a drug. This includes lists of drug compatibilities (for the purposes of administration), conversions and calculations, similar sounding drug names that are easily confused, tablets and capsules that should not be crushed, and the management of poisonings. Other resources included in this section may serve as an education tool rather than a quick reference, such as 'Identifying injection sites' and 'Preventing and treating extravasation'.

There are, however, some omissions in the Handbook, most notably paediatric indications and doses for a number of medications. No pharmacokinetic data are offered, which is a significant limitation of the book.

The Pocket guide presents the 'most frequently used' and 'clinically important' medications. It includes over 1000 medications so there are few significant oversights. There is also a brief section detailing some commonly used herbal medicines. There are some useful summary tables of varying preparations of the same drug (for example paracetamol), similar drugs frequently interchanged or of escalating potency or duration of action (for example steroids, insulins, local anaesthetics) and sound-alike drug names.

The value of the books is limited for Australian nurses by differing drug names, dosing schedules and different treatment practices between Australia and the USA. For example, adrenaline is referred to as epinephrine and is recommended as a treatment for asthma while salbutamol is not included in the book.

As with many pocket books the Guide is slightly larger than some handheld devices, while the content is more limited and is missing the functionality of an electronic resource. The conservation of space has resulted in some sections being difficult to follow because of the extensive use of abbreviations, symbols and brief point form. Furthermore, use of a very small font with few spaces has resulted in a very crowded looking text where detailed entries can be difficult to read. Other than price, the pocket guide is not likely to compare favourably with a handheld device.

The Handbook is supplemented with online resources which include software to download a full-text version for use on a handheld device. With increasing use of smartphones and other handheld devices, textbooks which make a version available for these media have a distinct advantage over texts which are only available in hard copy. The availability of a handheld device version may sway nurses to purchase this text over others. However, these features may not persuade those looking for an Australian reference or for more comprehensive pharmacokinetics.

Managing HIV in general practice

***Tom Turnbull**, General practitioner, O'Brien Street General Practice, Adelaide, and Clinical skills tutor, The University of Adelaide*

Summary

As a consequence of advances in care, life expectancy has significantly increased for many people with HIV. In Australia, the focus of care has shifted from acute illness and palliative care to chronic disease management. Many people with HIV receive much of their medical care from general practitioners. It is therefore important to know which problems can be managed in general practice and when these patients should be referred.

Key words: adverse effects, AIDS, travel, vaccination.

(Aust Prescr 2011;34:67–72)

Introduction

In 2009 it was estimated that 20 171 people were living with HIV in Australia.[1] As overall HIV infection numbers increase and uptake of more effective and less toxic antiretroviral therapy becomes more widespread, this population is going to increase and live longer. As a consequence, it is likely that more general practitioners will become involved in the care of people living with HIV. An understanding of the standard care, general management and medication-related issues is important.

To become a community prescriber of antiretroviral therapy for HIV, general practitioners need to complete an accredited training course. Details of training courses are on the Australasian Society of HIV Medicine website (www.ashm.org.au).

Standard care of a person with HIV

The aim of antiretroviral therapy is to achieve long-term control of HIV replication, enabling recovery and improved functioning of the immune system. The goal is to suppress the plasma viral load to below 40 copies/mL, which is the lowest point of detection in most routine assays.

Initiating therapy

Current guidelines[2] advise starting treatment if there is an AIDS-defining illness or a CD4 count below 350 cells/microlitre. There is some research (based on cumulative observational cohort data) to support earlier treatment for people with CD4 counts above 350 cells/microlitre,[3] but current opinion is divided on this.[4]

In certain circumstances, treatment is initiated regardless of the CD4 count[5] including:

- pregnancy
- rapid decline of CD4 cell counts
- active or high risk of cardiovascular disease
- high risk of HIV transmission, for example in serodiscordant couples
- treatment of co-infection with hepatitis B or C is indicated
- HIV-associated nephropathy
- malignancy
- certain opportunistic infections.

Regular monitoring

Treatment with antiretroviral therapy is generally lifelong and requires a great deal of commitment from patients, who require continued monitoring and support. There may be enduring adverse effects from earlier antiretroviral therapy in treatment-experienced patients. However, newer antiretroviral therapies are better tolerated and have less toxicity.

Most people with HIV see their doctor every three months for review and routine blood testing (Table 1). General practitioners can play a pivotal role in helping patients to address problems with their general health, adherence to medications, adverse effects of treatment, psychosocial wellbeing, broader preventive health and sexual health.

Adherence to treatment

It is vitally important that patients achieve close to 100% adherence to treatment to maintain viral suppression and minimise any risk of acquiring resistance to their antiretroviral therapy. A number of strategies to promote adherence have been trialled.[6] Increased alcohol use is a predictor for decreased adherence. State-based AIDS councils and People Living with HIV organisations have community and peer workers who are able to assist people with practical advice and counselling about HIV treatments (see Patient support organisation page 72).

Sexual health

Sexual health is an important issue in HIV management on many levels. The general practitioner should consider such issues as sexual behaviour and potential risk for HIV transmission as well as the risk of acquiring other sexually transmitted infections. Sexually active HIV-infected men who

Table 1

Routine laboratory testing for people with HIV [2,14]

Test	Recommendations
CD4 count and other T cell subsets	Every 3 months
HIV RNA (viral load)	2–8 weeks after starting antiretroviral drugs, then every 3 months
Complete blood count, biochemistry and liver function	Every 3 months
Fasting lipids	Every 6 months if borderline or abnormal, or annually if last measurement normal
Fasting glucose	Every 3 months if borderline or abnormal, or 6-monthly if last measurement normal
HIV resistance analysis – genotyping	At entry into care and at treatment failure (HIV RNA levels need to be >1000 copies/mL for testing)
Hepatitis B serology	At entry into care (If HBsAg positive, use tenofovir in regimen to treat both hepatitis B and HIV. If HBsAb negative, hepatitis B vaccination at 0, 1, 2 and 6 months using double dosage of vaccine)
Hepatitis C	Test if history of injecting drug use. Consider in male to male sexual transmission.
Urinalysis and urinary albumin creatinine ratio	Every 6 months to exclude HIV-associated nephropathy
Pregnancy testing	In women before starting on efavirenz
Sexual health check which may include: Pharyngeal swab – gonorrhoea NAAT/culture First void urine – chlamydia NAAT (in the presence of a urethral discharge, a swab for gonorrhoea culture would also be appropriate) Anal swab – gonorrhoea NAAT/culture and chlamydia NAAT Syphilis serology	Every 3–6 months depending on number of sexual partners and sexual behaviours
Pap smear	Annually
HLA–B*5701 testing for abacavir hypersensitivity	Before starting antiretroviral therapy

Table 1 adapted from references 2 and 14

HBsAg hepatitis B surface antigen HBsAb hepatitis B surface antibody

NAAT Nucleic Acid Amplification Testing

have sex with men should be tested for syphilis and other sexually transmitted infections during their routine check-ups (Table 1). Surveillance conducted in inner Sydney since 2006 shows a consistent pattern of 50–55% of all infectious syphilis notifications occurring in HIV positive men who have sex with men.[7]

Other issues relating to sexual health include the effect of ill health, depression and antiretroviral therapies on an individual's sexual functioning, for example erectile dysfunction, and the effect this may have on sexual relationships.

Mental health

Mental health problems, particularly depression and anxiety disorders, are common among people living with HIV. HIV-positive men have high rates of major depression – a study of gay men in urban general practice revealed that 32% of

195 men with HIV had major depression compared to 20% of 314 men who did not have HIV. However, HIV status was not independently associated with major depression. Rather, socio-economic hardship, interpersonal isolation and personal withdrawal were the major factors linked to depression in males.[8]

HIV can cause dementia and there is evidence that cognitive impairment develops earlier among people with HIV.[9] It impairs treatment compliance and adds to morbidity and mortality.

General practitioners are involved in the management of mental health problems, including pharmacotherapy, developing Medicare-funded mental health treatment plans with their patients and facilitating referral for psychological therapy.

Prophylaxis

Prophylaxis against *Pneumocystis jirovecii* pneumonia, usually trimethoprim with sulfamethoxazole, is recommended for patients with CD4 cell counts less than 200 cells/microlitre. Trimethoprim with sulfamethoxazole can also be used as prophylaxis against toxoplasmosis.

Patients with advanced immunodeficiency (CD4 cell count <50 cells/microlitre) should be considered for prophylaxis against *Mycobacterium avium* complex. Azithromycin is usually the best tolerated drug with fewest interactions.

Vaccinations

It is important for general practitioners to be familiar with recommendations around vaccinations (Table 2). This includes standard vaccinations, like influenza and pneumococcal, which are offered to patients with chronic conditions, hepatitis A and hepatitis B (in those who are not immune), as well as vaccinations relevant for travel.

Doctors should be aware that if the CD4 count is below 350 cells/microlitre, people might not respond adequately to vaccination. There are also safety issues around live vaccines such as MMR (measles, mumps, rubella), BCG (Bacillus Calmette-Guérin) and yellow fever*. If in doubt, specific guidelines are given in the Immunisation Handbook 9th edition,[10] or the treating HIV specialist can be contacted.

Travel

Some countries impose travel restrictions on people with HIV (http://hivtravel.org). Recently the USA has removed entry restrictions, which means that people living with HIV can now freely enter that country.

Chronic disease management

General practitioners are ideally placed to manage many of the complex issues facing the individual with HIV infection. A number of these problems are in fact familiar to general practitioners looking after people with any chronic condition.

* If travel to a yellow fever-endemic region by an immunocompromised person cannot be avoided, a medical exemption letter can be written. However, travel and quarantine regulations need to be checked.

Table 2
Vaccinations for people with HIV [15]

Vaccine	Recommendations
Hepatitis B	4 double dose injections, at 0, 1, 2 and 6 months
Influenza	Yearly
Pneumococcal	Should be given soon after HIV diagnosis. If CD4 count is <200 cells/microlitre when the vaccine is given, immunisation should be repeated when CD4 count is >200 cells/microlitre
Tetanus, diphtheria and pertussis	Repeat every 10 years
Hepatitis A virus	2 injections, at 0 and 6–12 months
Meningococcal oligosaccharide conjugate vaccine (tetravalent)	Recommended for all who are travelling to the meningitis belt in sub-Saharan Africa during certain times of the year
Rabies, typhoid (polysaccharide vaccine), oral cholera (inactivated)	Recommended if travelling to an endemic region. Equally applicable as HIV seronegative persons.

Management plans can assist in a number of ways by clarifying the issues for both the patient and doctor. They enhance communication and can facilitate appropriate referral to allied health practitioners and counsellors.

Cardiovascular disease

HIV is recognised to increase the risk of cardiovascular disease. Some antiretrovirals have been found to further add to this risk. Heart disease has been associated with abacavir use in an observational cohort. The protease inhibitor class and efavirenz are associated with lipid dysfunction. The HIV specialist may in some circumstances switch antiretroviral therapy to minimise this risk.

It is also important to manage other cardiovascular risk factors and lifestyle modification. Smoking cessation,[11] and improving diet and exercise should be encouraged. Drugs to reduce cholesterol can be used but caution should be taken due to potential drug interactions. Blood pressure should be managed according to current guidelines.

Diabetes

Abnormalities in glucose metabolism are common in patients on antiretroviral therapy. The aetiology is multifactorial and may involve antiretroviral drugs, patient factors (age, body mass index, family history) and perhaps even HIV infection itself. Antiretroviral treatment may lead to glucose abnormalities indirectly through their effects on body composition (peripheral lipoatrophy and central lipohypertrophy).

Current guidelines[2] suggest screening for diabetes before antiretroviral therapy is initiated, then at 3–6 months and annually after that. Recommendations for monitoring the microvascular complications of diabetes in patients with HIV are the same as for the general population.

The benefits of lifestyle modification in patients with HIV have not been evaluated. However in a small randomised trial of HIV patients with metabolic syndrome, intensive lifestyle changes were associated with significantly reduced HbA1c.[12]

Neurological conditions

Painful peripheral neuropathy can develop as a consequence of HIV infection or as an adverse effect of some antiretroviral therapies such as didanosine and stavudine. Treatment options for painful symptoms include gabapentin, tricyclic antidepressants or narcotic analgesia.

Efavirenz can cause sleep disturbance, anxiety and depression. Most symptoms diminish or disappear within 2–4 weeks of the first dose. Advise the patient to expect adverse effects and that they will probably settle. A short course of benzodiazepines can assist with the unsettling symptoms in the first two weeks. A shorter-acting drug with fewer metabolites is preferred, such as oxazepam, lorazepam or temazepam.

Osteopenia and osteoporosis

These conditions can be associated with androgen deficiency, low body weight and the use of tenofovir. As the cohort of people living with HIV ages, these conditions will become more prevalent.[13] Consider assessing fracture risk (see www.garvan.org.au/bone-fracture-risk or www.shef.ac.uk/FRAX), and bone mineral density after any fracture following minimal trauma. Encourage weight-bearing exercise and ensure adequate intake of calcium and vitamin D. Hormone replacement may be considered in hypoandrogenous states. Diagnosed osteoporosis should be actively treated. There are no known interactions between bisphosphonates and drugs used to treat HIV.

Renal disease

HIV can cause nephropathy. Contact an HIV specialist should any concerns arise.

Liver disease

Eleven percent of people living with HIV in Australia are co-infected with hepatitis C, 6% with hepatitis B, and 1% have both hepatitis C and hepatitis B. It should be remembered that antiretroviral use (that is, nevirapine and darunavir) can be associated with hepatotoxicity. Transaminase elevation can occur with most antiretroviral therapy. Exclusion of other causes of liver disease and monitoring of liver function are required. Consider alcohol intake as well. Atazanavir commonly causes hyperbilirubinaemia for which no action is required.

Gastrointestinal intolerance

The protease inhibitors lopinavir/ritonavir, fosamprenavir and ritonavir are associated with diarrhoea. Psyllium, loperamide or diphenoxylate/atropine can be trialled to relieve symptoms.

Lipodystrophy

Some antiretroviral drugs have been implicated in the development of redistribution of fat. Lipoatrophy (loss of fat from face and limbs) causes psychological distress. An injectable poly-L-lactic acid is available on the Pharmaceutical Benefits Scheme for the treatment of severe facial lipoatrophy. Practitioners who are trained and registered to perform this procedure are listed at www.lipoatrophy.com.au.

Effects to look out for that may be related to medications

Haematology

Zidovudine and other antiretrovirals are associated with a benign increase in mean cell volume. This is not harmful, but other causes need to be considered and excluded. Zidovudine can also cause life-threatening haemolytic anaemia and bone marrow suppression.

HIV infection causes thrombocytopenia which can respond to antiretroviral therapy.

Drug interactions

Antiretrovirals interact with a wide range of drugs so check for potential interactions before adding a new drug – start low, go slow and monitor the patient closely. If a patient presents with an adverse event, check if they have recently started any new drugs.

It is important to be familiar with some of the potential drug interactions with antiretroviral therapy (see www.hiv-druginteractions.org). Common medications that interact are St John's wort (with protease inhibitors, efavirenz, etravirine, nevirapine and maraviroc) and fluticasone (with ritonavir). Ritonavir, commonly used to pharmacologically boost protease inhibitors, is a potent inhibitor of cytochrome P450 enzymes and has the potential to interact with many common medications. For example, ritonavir can increase the risk of Cushing's syndrome in patients taking inhaled corticosteroids. Conversely, nevirapine and efavirenz are potent inducers of cytochrome P450 *in vivo* and will reduce concentrations of drugs such as methadone and the combined oral contraceptive pill. Warfarin concentrations can increase or decrease with efavirenz and need to be closely monitored.

With statins, there is a potential for interactions through CYP3A4. When prescribing them, use the lowest starting dose and carefully monitor for adverse effects.

The solubility of atazanavir decreases as pH increases. If used concomitantly, proton pump inhibitors should not exceed a dose equivalent to omeprazole 20 mg daily and should be administered at least 12 hours before atazanavir. Proton pump inhibitors should not be given to treatment-experienced patients already taking atazanavir as plasma concentrations of atazanavir may be reduced and loss of efficacy and viral resistance can occur.

All protease inhibitors increase the concentration of phosphodiesterase type 5 inhibitors (for example sildenafil). If needed, start with the lowest dose of the erectile dysfunction drug and monitor for adverse effects.

Conclusion

The treatment of HIV infection continues to evolve and people with HIV are living longer. General practitioners are likely to need to become more involved in providing care to people with HIV using their skills to manage the problems associated with chronic medical conditions.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 91)

1. Ritonavir can increase the risk of Cushing's syndrome in patients taking inhaled corticosteroids.
2. Vaccination may not be effective in patients who have a CD4 count below 350 cells/microlitre.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

Managing HIV in general practice

Doctors treating patients with HIV should be cognisant of the oral problems that occur in these patients. While their immunological status is reasonable, the majority of these patients will not develop the classically recognised oral manifestations of HIV disease, such as florid pseudomembranous candidosis, Kaposi's sarcoma or oral hairy leukoplakia. However, the patients are likely to have oral problems associated with their long-term treatment.

A recent study assessed the long-term use of highly active antiretroviral therapy (HAART) on the oral health of HIV-infected patients. The multiple logistical regression analysis, controlling for duration of HIV infection, CD4 count, smoking habits and alcohol consumption, showed patients have a greater risk of developing oral lesions with long-term use than with short-term use of HAART.[1]

Patients with HIV can develop profound oral dryness with a resultant increase in traumatic mucosal ulceration and pain, as well as an increased likelihood of developing dental caries. Furthermore, these patients have an increased risk of periodontal disease, dental decay, oral infections and poor healing after periodontal treatment or extraction. It is advisable for the treating clinician to discuss with the patient the potential dental adverse effects of the long-term use of HAART. Early referral to a dentist for appropriate management is important, particularly for the establishment of an effective dental preventive program. The key to oral health management would be six-monthly reviews by a general or special-needs dentist with an interest and training in the dental management of patients with HIV.

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Patient support organisation

NAPWA, National Association of People living With HIV/AIDS

NAPWA is Australia's national peak organisation representing people living with HIV. Its website has a range of resources and links to its member organisations in every state and territory.

NAPWA promotes access to the latest treatments for those who need them. It produces educational resources, provides training in HIV medicine for community workers, and collaborates with healthcare professionals, researchers, government and pharmaceutical companies.

Contact

Website	www.napwa.org.au
National office	PO Box 917, Newtown, Sydney NSW 2042
Phone	(02) 8568 0300 or freecall 1800 259 666

There are member organisations in every state and territory. Contact the national office for up-to-date details.

Abnormal laboratory results

Testing for HFE-related haemochromatosis

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Summary

HFE-haemochromatosis is a genetic disorder resulting from mutations of the HFE gene. It primarily affects people of Northern European descent. Clinical manifestations result from the progressive deposition of iron into various organs including the liver. An elevated serum ferritin concentration greater than 300 microgram/L and a transferrin saturation of greater than 45% will identify almost all patients with HFE-haemochromatosis. HFE genotyping confirms the diagnosis. In some patients, liver biopsy may still be necessary as the degree of hepatic fibrosis has prognostic implications.

Key words: ferritin, iron, liver, transferrin.

(Aust Prescr 2011;34:73–6)

Introduction

HFE-haemochromatosis is the most frequent inherited cause of iron overload in humans. The condition is due to an inborn error of iron metabolism leading to inappropriately increased intestinal iron absorption. Its clinical manifestations result from progressive iron deposition in certain organs. It is important to identify individuals with HFE-haemochromatosis early in the course of their disease, as early intervention can prevent the development of complications. These include cirrhosis of the liver, cardiomyopathy, arthropathy and diabetes. Most patients are diagnosed following a presentation with nonspecific symptoms such as lethargy and fatigue, altered liver function tests, or a family history of haemochromatosis.

Genetics

The HFE gene is located on chromosome six. It codes for a cell surface protein which is involved in the regulation of iron metabolism. Mutations of the gene therefore disrupt normal iron metabolism.

HFE-haemochromatosis is the most common autosomal recessive disorder in Northern European populations with heterozygous carrier rates of 1 in 10 and homozygosity rates of approximately 1 in 300. Homozygosity for the C282Y mutation accounts for 80–90% of cases of HFE-haemochromatosis and compound heterozygosity (C282Y/H63D) is the next most common genotype.[1] Phenotypic expression is highly variable with only a minority of patients developing systemic complications of iron overload.

An Australian study of people of Northern European descent reported symptoms and signs of iron overload in 28.4% of males and 1.2% of females who were C282Y homozygous.[2] The same study found that symptomatic iron overload was rare among compound heterozygotes (0.2%).

Transferrin saturation

The first approach to diagnosing HFE-haemochromatosis is the assessment of indirect markers of iron stores. Fasting transferrin saturation is considered to be the most sensitive screening test for HFE-haemochromatosis.

An elevated fasting transferrin saturation greater than 50% in women and 60% in men of Northern European descent has a positive predictive value of 86% for the diagnosis of HFE-haemochromatosis.[3] Lowering the threshold transferrin saturation to 45% improves the sensitivity and negative predictive value, but reduces the positive predictive value. In an Australian population study, a value of 45% was able to correctly identify 98% of C282Y homozygotes.[4] However, using this value will also detect heterozygotes who do not need further investigations. Approximately 30% of C282Y heterozygotes have a transferrin saturation greater than 45%.

The combination of an elevated fasting transferrin saturation (greater than 45%) and an elevated serum ferritin has a negative predictive value of 97%. This exceeds the accuracy of either test used alone.[3]

Serum ferritin concentration

Raised serum concentrations of ferritin occur in a number of different conditions including iron overload. There are also several causes of iron overload (see box). In the setting of iron overload, the serum ferritin tends to reflect total body iron stores and generally increases with progressive iron loading.[5]

An Australian population-based study reported a sensitivity of 50% and specificity of 87% for serum ferritin concentrations greater than 300 microgram/L for the diagnosis of C282Y homozygosity.[6] Higher serum ferritin thresholds have been studied in an attempt to lower the rate of false positives and increase the positive predictive value for the detection of HFE-haemochromatosis. For example, a population-based study screening 29 699 people identified 59 patients with a serum ferritin concentration greater than 1000 microgram/L, of whom 24 had HFE-haemochromatosis with 20 people being C282Y homozygous.[7]

Serum ferritin concentrations greater than 1000 microgram/L are associated with a higher risk of cirrhosis and may be used as an indication for liver biopsy.[8] A French study reported a sensitivity of 98%, a specificity of 72% and a positive predictive value of 55% when using a serum ferritin concentration of 1000 microgram/L to predict the presence of severe fibrosis among C282Y homozygotes.[9] Similar findings have been reported in Australian and Canadian populations.[10,11] Other factors that increase the clinical probability of severe fibrosis include hepatomegaly, abnormal transaminase levels, age greater than 35 years and a history of excessive alcohol intake.

An isolated elevated serum ferritin is often seen with acute or chronic inflammation. Patients with an isolated elevated serum ferritin should therefore be evaluated for other causes before genetic testing is considered.[12] More than 90% of people in the general community who have an elevated serum ferritin will have one of the following diagnoses:

- systemic inflammation
- chronic alcohol consumption
- non-alcoholic fatty liver disease
- hepatocellular necrosis
- malignancy.

In these clinical conditions, serum ferritin concentration is usually less than 1000 microgram/L and is often accompanied by a normal transferrin saturation. This is a common clinical scenario and interpretation of these patients' iron studies is often compounded by the presence of heterozygosity for the HFE mutations. Despite the elevated serum ferritin concentration, the vast majority of these patients do not have significant iron overload and treatment of the underlying condition usually results in a decrease in the serum ferritin concentration. Moreover, serum ferritin concentration increases with age and is influenced by gender and physiological blood loss. Interpretation of serum ferritin concentration requires careful consideration of these characteristics in each patient.

Measuring C-reactive protein may help to exclude systemic inflammation if it is not clinically evident. Other tests such as serum aspartate transaminase, alanine transaminase, creatinine kinase, erythrocyte sedimentation rate, fasting glucose, and the lipid profile may also help to exclude other causes of an isolated elevated serum ferritin.

Box

Causes of iron overload

Hereditary haemochromatosis

- HFE-haemochromatosis
- non-HFE-haemochromatosis

Secondary iron overload

- multiple blood transfusions
- iron-loading anaemia (β-thalassaemia and sideroblastic anaemia)

Chronic liver disease

- hepatitis C infection
- alcohol-related liver disease
- non-alcoholic fatty liver disease
- porphyria cutanea tarda

HFE genotyping

The diagnostic evaluation of people with suspected HFE-haemochromatosis changed following the discovery of the HFE gene in 1996.[1] Blood tests for HFE genotyping should be considered in people with suspected iron overload, patients with a family history of HFE-haemochromatosis and cases of unexplained chronic liver disease with an increased transferrin saturation[12] (see Fig. 1). Genetic screening for HFE-haemochromatosis in the general population is not recommended because the disease penetrance is low.[12]

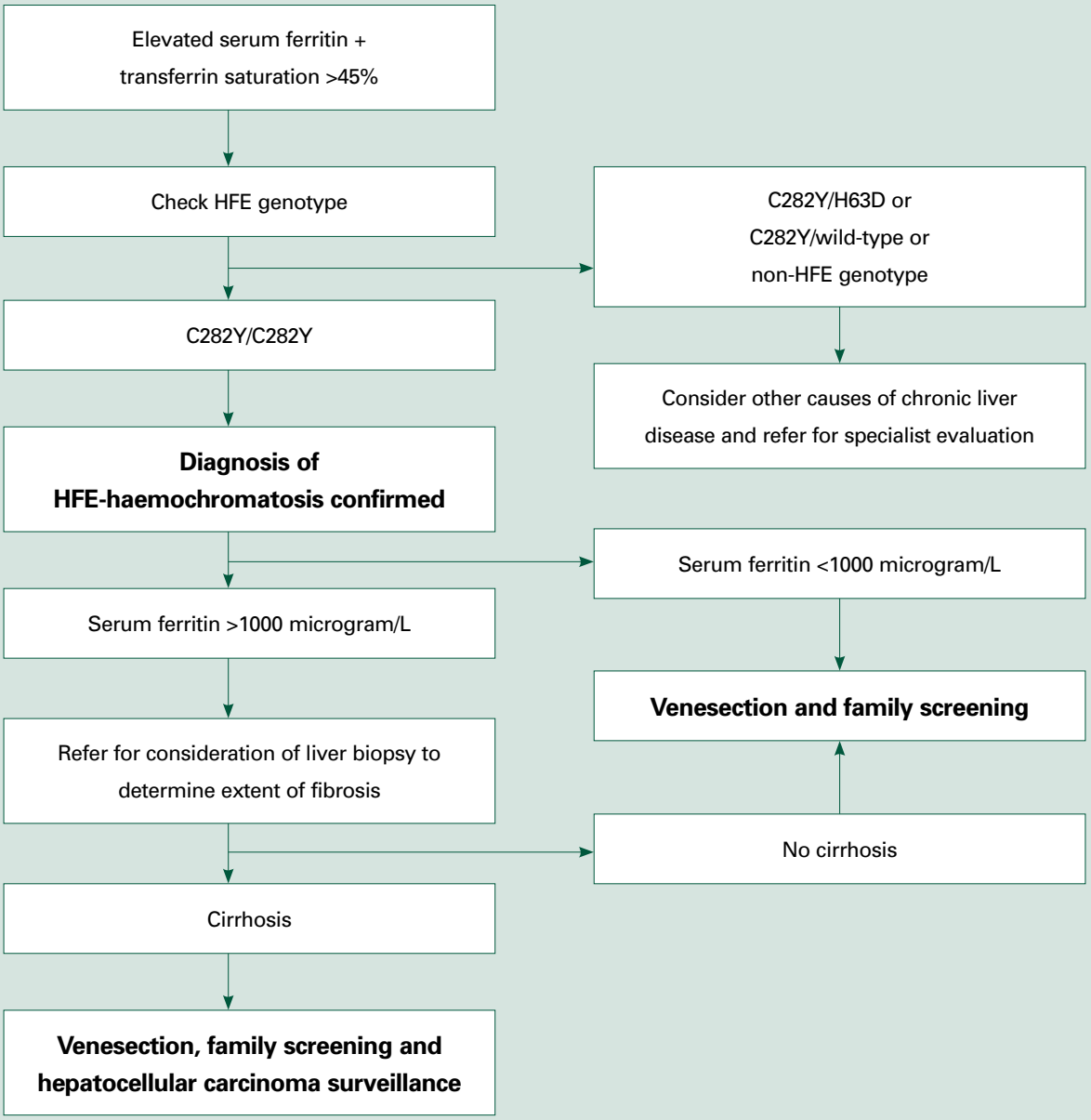
Most patients with HFE-haemochromatosis are C282Y homozygotes and the majority of the remaining cases are compound heterozygotes (C282Y/H63D). H63D homozygosity does not result in significant hepatic iron overload and an elevated serum ferritin in these patients is usually the result of hepatic steatosis or excess alcohol consumption.[13]

Other tests

Following the advent of HFE genotyping, liver biopsy is no longer necessary to make a diagnosis of HFE-haemochromatosis. However, liver biopsy is still required to stage hepatic fibrosis, especially as patients with serum ferritin concentrations greater than 1000 microgram/L are more likely to have cirrhosis.[9] Diagnosing the presence of cirrhosis in HFE-haemochromatosis is clinically important as affected patients have a significant risk of hepatocellular carcinoma and should enter a surveillance program. When the diagnosis of

Fig. 1

Algorithm for the diagnosis and management of HFE-haemochromatosis



iron overload remains unclear, liver biopsy or MRI may still be required to assess for hepatic iron overload.

The special form of MRI is a non-invasive method of directly assessing hepatic iron concentration. There is an excellent inverse correlation between the signalling and hepatic iron concentration.[14] The main limitation of this method is its inability to stage hepatic fibrosis. Transient elastography, a special form of ultrasound, may have a role in staging fibrosis as an alternative to liver biopsy.[15]

Family screening

Siblings of patients with HFE-haemochromatosis should undergo HFE genotyping as they have a 25% chance of being affected.[12] In clinical practice, most family members also have serum iron indices measured to assess their body iron stores. Whether individuals are screened depends upon several factors including their age and health status, and the attitudes of the family.[12] In the case of children who have a parent with HFE-haemochromatosis, HFE genotyping of the unaffected

parent may be of value.[16] In such cases, the likelihood of genetic susceptibility and the need for testing of children later in life can be established.

Conclusion

HFE-haemochromatosis is a common genetic disorder primarily affecting people of North European descent. Early diagnosis and treatment prevent progressive disease. It is important that people with characteristics associated with severe hepatic fibrosis or cirrhosis are identified and managed appropriately.

Recommendations

- Patients with suspected iron overload should first have their serum ferritin and fasting transferrin saturation measured.
- HFE genotyping should be carried out in all patients with an elevated serum ferritin and transferrin saturation.
- Diagnosis of HFE-haemochromatosis should not be based on C282Y homozygosity alone, but requires evidence of increased hepatic iron stores. People who are C282Y homozygotes with normal iron stores should undergo regular testing.
- Compound heterozygotes (C282Y/H63D) and H63D homozygotes presenting with an elevated serum ferritin should first be investigated for other causes of an elevated serum ferritin, in particular alcohol and non-alcoholic fatty liver disease.
- Liver biopsy should be offered to C282Y homozygotes with a serum ferritin greater than 1000 microgram/L as these patients are at risk of cirrhosis.
- As HFE-haemochromatosis is an autosomal recessive disease, genetic testing of siblings and other first degree family members is recommended.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 91)

3. The diagnosis of HFE-haemochromatosis requires a liver biopsy.
4. HFE-haemochromatosis is the most common cause of an isolated elevation of serum ferritin.

Treatments for snoring in adults

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Summary

Snoring is a symptom and sign of airway obstruction. Treatments for snoring should be based on the degree of associated sleep disordered breathing, symptoms of excessive daytime somnolence and disruption to family and social life. Lifestyle interventions such as weight loss and reducing alcohol intake help. There are many treatments with varying degrees of efficacy. Continuous positive airway pressure is the gold standard treatment for obstructive sleep apnoea, but in some instances a mandibular advancement splint or a surgical approach may be required.

Key words: continuous positive airway pressure, lifestyle modification, sleep apnoea, sleep disordered breathing.

(Aust Prescr 2011;34:77–9)

Introduction

Adult patients who snore are currently classified into four, albeit imperfect, groups including simple snoring, mild obstructive sleep apnoea, moderate obstructive sleep apnoea and severe obstructive sleep apnoea. This excludes more complex conditions such as central sleep apnoea and obesity-hypoventilation syndrome.

Moderate to severe obstructive sleep apnoea is associated with sudden death and significantly increased cardiovascular risk.[1] Effective treatment with continuous positive airway pressure (CPAP) reduces this risk.[2] There is also some evidence, although less well recognised, for surgery[3] and the use of mandibular splints.[4] To manage complicated cases, a multidisciplinary clinical team may be required.

Simple snoring and mild obstructive sleep apnoea are less likely to be associated with significant adverse cardiovascular events, but are still treated if patients are concerned socially or if they are excessively tired or waking unrefreshed.

Patients presenting with snoring need to be comprehensively assessed. This includes a history (see Box 1), full cardiovascular assessment, physical examination, and sleep study.

Lifestyle modifications

Weight

Obstructive sleep apnoea is strongly associated with obesity and the importance of weight loss is well recognised.[5] Personal trainers and dietitians can help patients with weight problems and concomitant cardiovascular risk factors, as well as surgical patients in whom subsequent weight gain or regain would be detrimental. Healthcare plans, such as the Enhanced Primary Care plans, can be highly advantageous in promoting shared care and follow-up of weight loss.

Bariatric surgery should be considered a valuable treatment, particularly when the body mass index exceeds 35 (surgical treatment for snoring is less effective for these patients). It may also be an option for obese patients who cannot tolerate CPAP.

Alcohol and other lifestyle factors

Alcohol consumption exacerbates snoring, and reducing or giving up alcohol should be advised. Other factors increasing cardiovascular risk such as smoking, diabetic control, hypertension and hypercholesterolaemia need to be addressed. Excessive daytime somnolence may relate to other sleep and medical disorders such as hypothyroidism, which can exacerbate sleep symptoms or fatigue.

Positional treatments

Sleeping on the side or in a more upright position rather than supine or prone is sometimes recommended but lacks strong evidence.

Over-the-counter remedies

As a general rule, over-the-counter remedies have limited proven efficacy in the treatment of snoring. Certainly significant

Box 1

Taking a history in patients with snoring

Snoring – loudness, duration, average number of nights per week
Partner witnessed sleep apnoeas
Sleep hygiene – sleep times
Waking refreshed or unrefreshed
Sleeping position – supine, lateral or prone
Daytime somnolence – symptoms
Motor vehicle or industrial accidents
Nasal symptoms, thyroid symptoms
Previous treatments (device, surgical) and outcomes
Weight
Partner or social disruption
Cardiovascular comorbidities, including family history

sleep apnoea needs to be excluded before trialling such remedies. Nasal strips may prove useful in establishing the degree of reversibility of dynamic external nasal valve collapse before pre-phase nasal surgery.

Continuous positive airway pressure

CPAP is the gold standard treatment for moderate to severe obstructive sleep apnoea[6] and is a viable treatment option in simple snoring and mild obstructive sleep apnoea. It can be applied via a nasal mask (with or without nasal pillows) or full face mask, and a fixed or fluctuating pressure can be used.

A functional nasal airway is an absolute requirement for CPAP, and in many instances medical (usually nasal sprays), immunological (allergy desensitisation)[7] and surgical treatments for the nose may be necessary.

Compliance

Estimates suggest that 30% or more of patients cannot or will not use CPAP in the long term. These patients can be considered for either counselling to promote CPAP use, contemporary surgical airway reconstruction or a mandibular advancement splint.

Mandibular advancement splint

This is an intraoral appliance designed to improve or cure snoring by increasing the retrolingual airway and, due to the tongue's attachment to the soft palate via palatoglossus and overlying mucosa, may even improve the retropalatal airway (see Fig. 1). A mandibular advancement splint can relieve up to 90% of simple snoring and mild obstructive sleep apnoea cases, but long-term compliance rates are generally only around 50–60%.

A mandibular advancement splint is a viable alternative in moderate to severe obstructive sleep apnoea when CPAP has failed, but success rates are considered less. In some instances, surgery and device use may be combined to improve efficacy, but mostly single modality treatment is preferred. It is appropriate for patients with moderate to severe disease to undergo a sleep study with a fitted mandibular advancement splint *in situ* to establish device efficacy.

Recent evidence[8] supports appropriate fitting of devices by trained dentists rather than the so-called 'boil and bite' self-fitted splints. Annual follow-up with a dentist to reduce temporomandibular adverse effects is generally advised.

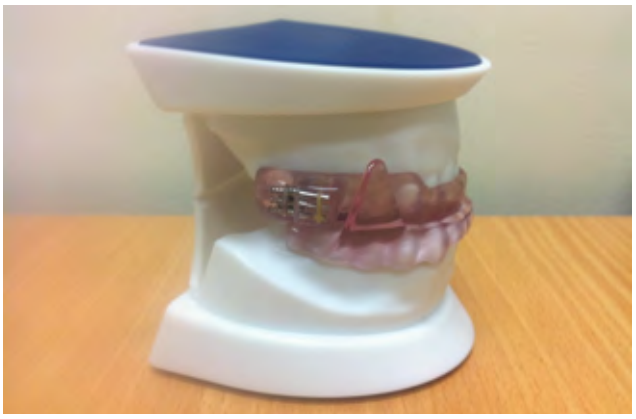
Pre-phase nasal surgery

Pre-phase nasal surgery is designed to facilitate subsequent treatments such as CPAP. It is rarely intended to cure snoring in isolation. It may involve a combination of septoplasty or septal reconstruction, turbinate reduction, functional endoscopic sinus surgery, external nasal valve or tip surgery, rhinoplasty and rarely in adults, adenoidectomy. Many patients require ongoing treatment with steroid nasal sprays and salt water rinses, even after nasal surgery, to maintain optimal nasal patency.

Fig. 1

Mandibular splint

A Splint open



B Splint closed

Surgical options

Surgery is a valid treatment option in sleep disordered breathing,[5] although health professionals are often uncertain about when and who to refer (see Box 2).

Surgical treatment options are multiple and often staged, despite patient perceptions that a single procedure will be curative. Tonsil and tongue size have implications for surgery. In

Box 2

When to refer patients with snoring or obstructive sleep apnoea for surgery

- Failed continuous positive airway pressure or device use
- Favourable anatomy for surgery e.g. tonsillar hypertrophy
- Patient desires surgery/unwilling to use device
- Patient requires pre-phase nasal treatment to facilitate further therapies
- Significant craniofacial abnormalities (maxillofacial surgeon)

patients with large tonsils (grade 3 or 4) and favourable tongue size (small – grades 1 or 2), modified uvulopalatopharyngoplasty with bilateral tonsillectomy should be considered, and in my opinion should be considered the gold standard treatment.[9] Some lesser tonsillar grades and unfavourable tongue sizes may still be considered for modified uvulopalatopharyngoplasty and radiofrequency ablation when device use has failed and where positional snoring manoeuvres and other findings suggest improvement or cure can be achieved.

In patients with less favourable tonsillar size and palatal anatomy, transpalatal advancement with uvulopalatopharyngoplasty has proven efficacious in increasing the size of the retropalatal airway, and reducing critical closing pressure.[10] This will often be combined with multichannel tongue radiofrequency *or* radiofrequency and lingual tonsillectomy *or* tongue reduction (such as submucosal lingualplasty) *or* geniotubercle advancement (tongue tensing operation), depending on expert assessment by a specialist trained in contemporary airway reconstruction techniques.

Maxillomandibular advancement, performed by skilled maxillofacial surgeons, remains a surgical option. It may be appropriate in device use failure or rejection where either soft tissue surgical techniques have resulted in incomplete cure *or* significant craniofacial structural anomaly exists precluding soft tissue surgical protocols.

Conclusion

Sleep disordered breathing, including snoring and obstructive sleep apnoea, represents a heterogeneous condition and as such requires multidisciplinary input. It can have significant adverse health consequences and for patients who cannot tolerate CPAP, other treatment options should be offered. Mandibular splints and surgery are valid alternatives.

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Dr MacKay has attended ArthroCare Coblation conferences paid by ArthroCare.

Self-test questions

The following statements are either true or false (answers on page 91)

5. If tolerated, mandibular advancement splints often relieve mild obstructive sleep apnoea.
6. Continuous positive airway pressure is effective for moderate to severe obstructive sleep apnoea.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

Treatments for snoring in adults

There has been a significant rise in the use of intraoral devices for the treatment of snoring and sleep apnoea. Dentists have an increasing choice of mandibular advancement splints to provide for their patients. Currently, no single device has been proven more effective than another.[1] Success is strongly associated with patient compliance.

Patients with mild to severe sleep apnoea can have good long-term outcomes with these devices. The reduction in the apnoea/hypopnoea index, as measured during sleep studies, can be up to 60%.[1] However, our ability to predict success in any individual patient is limited. Currently there is no individual measure or clinical tool that can be used as a predictor of success. This needs to be clearly outlined to potential users.

Further, the effect on the dentition and the temporomandibular joint after long-term use can occasionally be considerable. Patients therefore need to be carefully followed and fully informed of all potential consequences of these devices.[1]

For patients with sleep apnoea who cannot use continuous positive airway pressure (CPAP) devices, intraoral mandibular advancement splints can be of value. Treatment of sleep apnoea with CPAP devices has been shown to have a profound effect on both the quality of life and life expectancy.[2] Presumably, treatment of sleep apnoea with intraoral appliances will have similar beneficial effects, however this has not as yet been shown.

The Australian Dental Association's policy on the use of dental appliances to treat sleep disorders clearly states that dentists should not provide these devices without the patient having a prior specialist (respiratory or ENT) diagnosis. A team approach to the management of these patients with mandibular advancement devices is essential.

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Your questions to the PBAC

Lamotrigine for bipolar disorder

Could you please review listing lamotrigine on the Pharmaceutical Benefits Scheme (PBS) as a treatment for bipolar disorder. Lamotrigine is a well established mood stabiliser and maintenance treatment for bipolar disorder. Patients with this severe mental illness have to pay $80 to $200 a month for this medication. These patients are very often unable to work due to their illness and this treatment is out of the reach of many.

Elvera Stow
General practitioner
Narre Warren, Vic.

PBAC response:

Lamotrigine is currently listed on the PBS for treatment of epileptic seizures which are not adequately controlled by other antiepileptic drugs. Of the eleven brands of lamotrigine currently listed, none have marketing approval from the Therapeutic Goods Administration (TGA) for use in bipolar disorder.

The Pharmaceutical Benefits Advisory Committee (PBAC) has previously considered several submissions for a brand of lamotrigine that has TGA marketing approval for prevention of depressive episodes in patients with bipolar disorder, most recently in March 2005. However, it has not been provided with the necessary evidence to show cost-effectiveness in this patient group and therefore lamotrigine has not been recommended for PBS listing for this indication. The manufacturer is welcome to submit further information for consideration by the PBAC at any time.

The PBAC meets three times a year in March, July and November. Since July 2005, Public Summary Documents providing information of the PBAC's deliberations for major and selected minor submissions have been published on the website approximately four months after each meeting at: www.health.gov.au/internet/main/publishing.nsf/Content/public-summary-documents-by-meeting. You may wish to consult these pages for details of PBAC submissions.

Do you have a question for the PBAC?

Australian Prescriber readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee (PBAC). The journal publishes selected questions from readers, together with answers from the PBAC. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings and withdrawals.

This exclusive arrangement helps *Australian Prescriber* readers understand how the contents of the Schedule of Pharmaceutical Benefits (www.pbs.gov.au) are determined.

Letters and responses are reviewed by our Editorial Executive Committee and may be edited before publication. It may not be possible to reply to all individual questions.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update Volume 2, Number 3, June 2011

Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/hp/msu.htm

In this issue:

Risk of hypomagnesaemia with proton pump inhibitors

Summary

A recent international safety advisory has warned of a potential association between prolonged use of proton pump inhibitors (PPIs) and serious hypomagnesaemia-related adverse events such as tetany, seizures, delirium and cardiac arrhythmias. While this occurs rarely, prescribers should be vigilant to PPI-associated hypomagnesaemia. Patients presenting with hypomagnesaemia may require PPI discontinuation.

Proton pump inhibitors (PPIs) are among the most widely used classes of drugs in Australia, with more than 130 million Pharmaceutical Benefits Scheme prescriptions dispensed since 1992.

Suspected PPI-induced hypomagnesaemic hypoparathyroidism was first reported in the literature in 2006, based on two cases identified in Australia.[1] To March 2011, the TGA had received 2545 reports of suspected adverse reactions to PPIs, six (0.2%) of which were reports of hypomagnesaemia. In five cases, the PPI was the only suspected medication and serum magnesium levels returned to normal after the PPI was discontinued. In two of these cases a subsequent fall in serum magnesium levels was reported after an alternative PPI was prescribed. The underlying mechanism is unclear; however, extrarenal magnesium wasting by impaired intestinal magnesium transport or intestinal loss has been proposed.[2]

The presentation of patients with mild-to-moderate hypomagnesaemia may be asymptomatic or non-specific. Patients with severe hypomagnesaemia often have coexistent hypokalaemia and hypocalcaemia, which can contribute to potentially life-threatening sequelae such as tetany, seizures and cardiac arrhythmias, and may not be easily corrected without magnesium supplementation. For several of the cases reported in the literature, magnesium supplementation was only partially effective at correcting the hypomagnesaemia while PPIs were continued.[3] For further information on magnesium homeostasis and abnormalities, see the overview in *Australian Prescriber*.[4]

While most of the TGA reports and those analysed recently by the US Food and Drug Administration occurred in patients who had been taking a PPI for longer than one year,[5] there is no way to reliably predict those who may be at higher risk. Other medications (e.g. loop and thiazide diuretics) may cause or worsen hypomagnesaemia. Prescribers should be vigilant to the potential risk of hypomagnesaemia in patients requiring long-term PPI treatment. Patients developing hypomagnesaemia may require PPI discontinuation.

References

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Use of 2011 seasonal influenza vaccines in children

Summary

The 2011 seasonal influenza vaccines vary in their approved indications and recommendations for use in children. These variations relate to the availability of Australian safety information for the vaccines and the ability of sponsors to meet requirements for active surveillance of children. The TGA requests that consumers and healthcare professionals report all adverse events associated with influenza vaccination in patients of any age and any instances of inadvertent administration to a child of a vaccine not currently recommended for use in children, regardless of whether the child has a reaction.

During the 2010 influenza season an excess number of cases of febrile reactions and febrile convulsions was observed in paediatric populations following immunisation with one of the registered seasonal trivalent influenza vaccines.[1] Consequently, the TGA imposed a condition on the registration of all 2011 seasonal influenza vaccines with a paediatric indication which were not supplied in Australia in 2010. Sponsors were required to undertake active surveillance of children from six months to nine years of age, to ensure effective monitoring of paediatric populations in Australia previously unexposed to these vaccines.

Two sponsors were unable to meet this condition of registration. Although the safety of Agrippal and Fluarix has been demonstrated in the Northern Hemisphere 2010–11 influenza season, the TGA does not have any safety data on the use of these vaccines in Australian children. Hence, the TGA recommends that these vaccines are not used in any child under the age of nine years.

For children under the age of nine years it is recommended that they be vaccinated with either Influvac or Vaxigrip. These two vaccines were not associated with increased rates of fever or febrile reactions in 2010.

CSL's vaccine Fluvax is not approved for use in children under the age of five years for the 2011 influenza season. Although CSL has an active surveillance system in place to actively monitor children aged 5–18 years, the Australian Technical Advisory Group on Immunisation (ATAGI) has advised that there is a strong preference for the use of either Vaxigrip or Influvac in children aged five years to less than 10 years. ATAGI advises that Fluvax may be used in children aged five years to less than 10 years when no timely alternative vaccine is available.[2]

The approved indication for each seasonal influenza vaccine and the recommendations for their use in children are found in the table below.

The TGA requests that consumers and healthcare professionals report all adverse events associated with influenza vaccination in patients of any age. Healthcare professionals are also requested to report any inadvertent administration to a child of a vaccine not currently recommended for use in children regardless of whether the child has a reaction. See 'What to report' on page 84 for further information – inadvertent administration can be reported in the same way as adverse reactions.

References

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2. Australian Technical Advisory Group on Immunisation. Clinical advice for immunisation providers regarding the administration of 2011 trivalent seasonal influenza vaccines. Canberra: ATAGI; 2011. www.immunise.health.gov.au/internet/immunise/Publishing.nsf/content/immunise-atagi-vaccine-advice [cited 2011 May 4]

Vaccine	Sponsor	Approved indication	Recommendations for use in children
Fluvax	CSL	5 years +	Not approved for use in children under 5 years There is a strong preference that Vaxigrip or Influvac be used in children under the age of 10 years*
Influvac	Abbott	6 months +	Use in children aged 6 months and above
Vaxigrip	Sanofi Pasteur	6 months +	Use in children aged 6 months and above
Intanza	Sanofi Pasteur	18–59 years	Do not use (approved for adults aged 18–59 years only)
Fluarix	GSK	6 months +	Not recommended in children under the age of 9 years
Agrippal	Novartis	6 months +	Not recommended in children under the age of 9 years

* CSL has an active surveillance system in place to actively monitor children aged 5–18, however ATAGI has advised that there is a strong preference that Influvac or Vaxigrip be used in children under the age of 10 years

Investigation of Prevenar and deaths in children in Japan: what does it mean for Australia?

Summary

In response to the suspension of Prevenar and ActHIB in March 2011 in Japan due to a potential link with childhood deaths, the TGA conducted an investigation finding no safety signal for an association between Prevenar and death in Australia. As a result, the registration and recommendations for use of Prevenar are unchanged. This article describes the process used by the TGA to investigate this potential safety concern.

On 7 March 2011, Japan's Health Ministry suspended the use of two paediatric vaccines, Prevenar and ActHIB, following reports of the death of four children who had recently been immunised with these vaccines. Both Prevenar and ActHIB are registered in Australia, although ActHIB has not been supplied in this country. Prevenar, a pneumococcal conjugate vaccine (7vPCV), has been supplied under the National Immunisation Program since 2005 for children at ages 2, 4 and 6 months.

A search of the TGA's Adverse Drug Reactions Database using the terms 'Prevenar' (medicine tradename) and 'death' or 'death maybe drug' (outcome) identified five cases. For these five reports, the age at death ranged from 2 to 4 months, the dates of death from 2002 to 2010, and concomitant vaccine was administered in all cases (Infanrix and/or rotavirus vaccine).

Further information, including hospital records (discharge summary) and coroners' reports, was collected for each of these cases by contacting the initial reporter of the event. A causal association between Prevenar and the adverse event of death was determined to be unlikely for four of the five cases. These assessments were based on the length of time between vaccination and event, the detailed description of the circumstances surrounding the event, coroners' report and past medical history. For the remaining case, the initial description suggested that causality was unlikely, and we are continuing our follow-up to obtain verifying information.

Approximately 4 million doses of Prevenar (an average of 800 000 per year over five years, based on data from Medicare Australia and the Australian Childhood Immunisation Register) were given in Australia between 1 January 2005, when Prevenar was included on the National Immunisation Program for all children under two years of age, and March 2011.

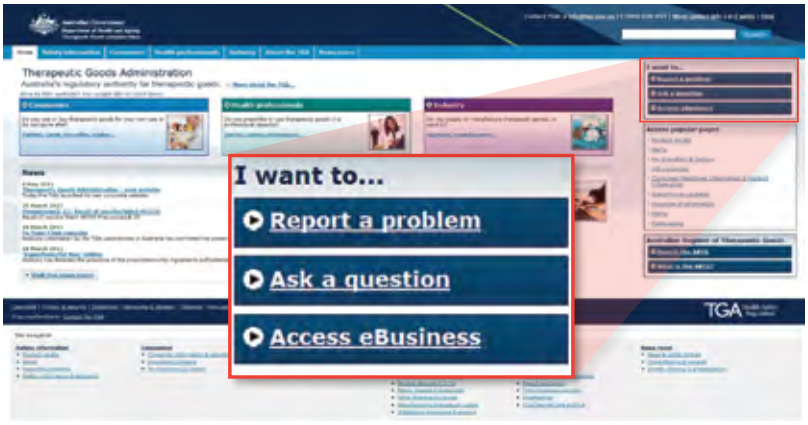
The TGA has concluded that there is no evidence of a causal association between Prevenar and deaths in children in Australia. The TGA's finding is consistent with that of a Japanese advisory panel, which also found no direct causal association between the deaths and the vaccines. The suspension of these vaccines is expected to be lifted in Japan.

This is an example of many similar investigations the TGA conducts using the Adverse Drug Reactions Database and other resources in response to safety concerns raised internationally and nationally, to determine the appropriate action required, if any, in Australia.

Finding information about adverse reaction reporting on the new TGA website

In early May, the TGA launched its new website at www.tga.gov.au. The website improves access to important information on the safety and regulation of medicine in Australia.

The new site makes it easier to find the 'blue card' adverse reaction reporting form and links to information about reporting online or to the Adverse Medicine Events Line for consumers. From the home page, click on 'Report a problem' on the right of the page (see figure) or choose 'Reporting problems' from the 'Safety Information' menu at the top of the page.



Medicine recalls in Australia

Summary

A medicine can be recalled when a deficiency is identified in its quality, safety or efficacy.

There are about 40 medicine recalls each year in Australia. Medicines are recalled when a deficiency is identified in their quality, safety or efficacy. This might include simple labelling or packaging errors, or a more serious increase in unexpected adverse effects.

Recalls in Australia are often initiated by sponsors when they become aware of a problem with a product. Companies wishing to recall their medicine in Australia contact the TGA to discuss their proposed recall strategy and communication plan. The Australian company has the prime responsibility for the conduct of the recall by contacting suppliers and recovering product. The TGA's role is to review reports on the recall supplied by the company. The TGA can take further action if the recall is not progressing satisfactorily.[1]

Most recalls can be traced back to a single incident within the product's manufacturing site. The majority of recalls are batch-specific and companies are readily able to supply replacement batches that are not defective.

In most cases, defective batches are recalled from wholesalers or pharmacies. If the risks posed by the product defect are unacceptable the company will attempt to recover product from consumers. Only 10% of medicine recalls in Australia are conducted at a consumer level. In such recalls companies normally place recall notices in national newspapers and provide information to pharmacists and doctors who may have sold or prescribed the medicine. For example, in 2010 batches of two medicines were recalled because of concerns that cartons may have included tablets of a different strength. In both cases, letters were sent to pharmacists and notices were placed in newspapers.

In December 2010, Pfizer Australia Pty Ltd initiated a recall of sitaxentan (Thelin), used for pulmonary hypertension, following a safety review that found that the benefits of sitaxentan no longer outweighed the risks. In the first stage of the recall, wholesalers were notified to cease distribution of the medicine to pharmacies, and the sponsor informed pharmacies and prescribers of the need to start switching patients to alternative therapies. In the second stage, a recall notice was issued to retail and hospital pharmacies requesting them to return the product. The two-staged approach allowed time for patients to switch safely to an alternative therapy.

Further information about recalls and notices for some consumer-level recalls in Australia are available from the TGA website (www.tga.gov.au).

Reference

1. Uniform Recall Procedure for Therapeutic Goods. Canberra: Therapeutic Goods Administration; 2004. www.tga.gov.au/pdf/recalls-urptg.pdf [cited 2011 May 10]

Medicines Safety Update is written by staff from the Office of Product Review. Editor: Ms Elspeth Kay. Principal Medical Advisor: Dr Megan Keaney. Contributors to this issue include Mr Trevor Byrne, Dr Kerryn Coleman, Dr Kevin Dodd and Dr Katherine Gray. For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114.

What to report? You do not need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of all suspected reactions to new medicines, all suspected medicines interactions, and suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

Finding independent information on new drugs

***Rosalind Tindale**, Drug information specialist, Sydney*

Summary

When a new drug becomes available, prescribers may wish to have independent information to formulate their own opinion about its place in therapy. Information may be in the form of drug monographs or summaries, peer-reviewed articles, clinical guidelines, systematic reviews and clinical evaluations from drug agencies. Knowing where to find information on potential adverse drug reactions is important.

Key words: drug information, drug therapy, evidence-based medicine.

(Aust Prescr 2011;34:85–8)

Introduction

Prescribers may feel besieged by information when a new drug is marketed or listed on the Pharmaceutical Benefits Scheme. This information may take the form of glossy brochures, for instance, reports of conference proceedings or presentations at meetings. These publications have often been prepared by the manufacturer, or at least with funding provided by the manufacturer. Prescribers and pharmacists may want to find independent information on a new product.

Some sources of information are freely available online, while others may only be available by subscription or through state health department sites or libraries.

Drug-specific information

Following the registration of a new drug in Australia, the Therapeutic Goods Administration (TGA) publishes the Australian Public Assessment Report (AusPAR) free online (www.tga.gov.au/industry/pm-auspar.htm). This includes information about the clinical evaluation by the TGA, as well as the product information. Other national drug agencies provide similar assessments of new drugs online (Table 1). These are often available before the AusPAR, depending on when the drug is approved overseas, although formulations may differ.

A report of decisions made by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) also becomes available online following its meetings (www.health.gov.au/internet/main/publishing.nsf/Content/pbac-outcomes-and-public-summary-documents).

Once a product is marketed, the approved prescribing information becomes incorporated into practice software systems and is generally available through organisations such as MIMS and Health Communication Network.

Drug summary reports appear in independent publications such as NPS (National Prescribing Service) RADAR and *Australian Prescriber* (Table 2). Reviews of the product may also be found in other peer-reviewed journals (Table 3). There are publications designed for hospital formulary decision makers (Table 4).

Extensive monographs on new generic products, prepared by independent organisations, become available from sources such as AHFS Drug Information and DRUGDEX (Micromedex) (Table 5). Most of the resources listed in Tables 2–5 are published both in print and online. However, DRUGDEX is only available in electronic form.

Place in therapy

Prescribers may wish to confirm a drug's place in therapy by finding current disease management guidelines or evidence-based reviews.

Australian information

The Therapeutic Guidelines series and the Australian Medicines Handbook are major sources of information (Table 3). However, if any of these particular guidelines are a little dated or do not provide specific information about the drug of interest, it may be necessary to search further. *Australian Prescriber* and the various other NPS publications such as RADAR also provide guidance on the place of new drugs in therapy and are free (Table 2).

Table 1
National drug agencies

Organisation	Website
Therapeutic Goods Administration	www.tga.gov.au
US Food and Drug Administration	www.fda.gov
UK Medicines and Healthcare Products Regulatory Agency	www.mhra.gov.uk
Canadian Agency for Drugs and Technologies in Health	www.cadth.ca
European Medicines Agency	www.ema.europa.eu

Table 2

Freely available information on new drugs

Source	Access	Comments
NPS publications including:	www.nps.org.au	Provides independent drug information
-*Australian Prescriber*	www.australianprescriber.com	Peer-reviewed journal publishing concise reviews on drugs and therapeutics. Reviews are usually published when new drugs first become available for prescribing. Six issues a year in print and online.
-NPS RADAR	www.nps.org.au/health_professionals/publications/nps_radar	Provides a review of evidence on new drugs when they are listed on the Pharmaceutical Benefits Scheme. Reviews give key practice points and place in therapy. Three issues a year with extra reviews on the web. Available in print, online and with certain prescribing software.
Articles from open-access publishers	e.g. www.dovepress.com, www.biomedcentral.com	Provide online access to articles from peer-reviewed biomedical and scientific journals

International consensus guidelines and evidence-based reviews

Open access websites

Valuable websites which provide a wide search function for international guidelines and evidence-based reviews include:

- Trip Database www.tripdatabase.com
- Health Information Resources, UK NHS Evidence www.library.nhs.uk
- PubMed www.ncbi.nlm.nih.gov/pubmed

PubMed contains Medline and provides journal citations, abstracts and the full text of selected articles. Searches can be limited to publication type, for example 'practice guideline', 'consensus development conference', 'evidence-based practice', 'guideline', 'meta-analysis' or 'review'. The PubMed Clinical Queries search page (www.ncbi.nlm.nih.gov/pubmed/clinical) is particularly useful for finding an array of clinical evidence and consensus documents.

Searches of these sites can identify systematic reviews from such organisations as the Cochrane Library and guidelines from international groups including the National Health and Medical Research Council in Australia, the New Zealand Guidelines Group, the National Institute for Health and Clinical Excellence in the UK and the Scottish Intercollegiate Guidelines Network. Documents available through the US National Guideline Clearinghouse can also be accessed. Other useful free-access sites include eMedicine (www.emedicine.medscape.com) and Intute: Medicine (www.intute.ac.uk/medicine).

Websites accessed by subscription only

Various evidence-based medicine resources may also be available through state health departments or university and hospital libraries:

- Evidence-Based Medicine Reviews can be accessed through Ovid (for example via Medline, limiting the search to Evidence-Based Medicine Reviews). This resource covers a number of major evidence-based medicine databases including the Cochrane Library.
- UpToDate www.uptodate.com is an excellent peer-reviewed clinical information resource. With the help of editors, topics are written by clinicians for clinicians. The information is current and includes particular categories for primary care.
- DynaMed www.ebscohost.com/dynamed is another excellent clinical reference tool for healthcare professionals designed to be used at the point of care.

Other well-regarded resources for evidence include:

- Essential Evidence Plus www.essentialevidenceplus.com
- Clinical Evidence www.clinicalevidence.bmj.com
- American College of Physicians PIER http://pier.acponline.org
- FirstConsult www.firstconsult.com

Updating information

Information can be updated by searching databases such as Medline (for instance via PubMed) and Embase. At the beginning of the PubMed search results, articles may appear ahead of publication. These may be similar to those found from searching Ovid's Premedline. Ovid's user-friendly searching of Medline, Premedline (Medline-in-Process) and Embase is available via several state health departments' clinical information sites.

Table 3

Subscription-only information on new drugs *

Source	Access	Comments
Australian Medicines Handbook (AMH)	Available in electronic (www.amh.net.au) and print formats	Concise drug summaries with practice points, counselling information, comparative drug information tables and prescribing guides. Updated twice a year in electronic version and annually in print. AMH is jointly owned by the Royal Australian College of General Practitioners, the Pharmaceutical Society of Australia and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists.
Therapeutic Guidelines	Available in electronic (www.tg.org.au) and print formats	Provides independent evidence-based guidelines for prescribing by specialty. Guidelines for each specialty are updated every few years.
AusDI Advanced	Distributed by Health Communication Network	Standardised summary monographs together with the approved prescribing information
Martindale: The Complete Drug Reference	Available in hard copy or electronically. Sources include Micromedex and Medicines Complete.	Produced by the publishing arm of the Royal Pharmaceutical Society of Great Britain
Drug bulletins:†		
-Drug and Therapeutics Bulletin	www.dtb.bmj.com	Published by the BMJ group in the UK
-The Medical Letter on Drugs and Therapeutics	http://medicalletter.org	Based in the USA
-Prescrire International	http://english.prescrire.org/en	Based in France
Reviews in journals such as:		Provide extensive drug reviews. Check whether authors have received financial support from the pharmaceutical manufacturers. Journal supplements are often supported by the manufacturer of a new therapy.
-The Annals of Pharmacotherapy	www.theannals.com	
-Pharmacotherapy (some articles are free)	http://pharmacotherapyjournal.org	
-Drugs, Drugs and Aging, BioDrugs	http://adisonline.com	
Additional resources:		Some of these products are designed to support point-of-care decisions
-Lexicomp	www.lexi.com	
-Clinical Pharmacology	www.clinicalpharmacology.com	
-Facts & Comparisons	www.factsandcomparisons.com	

* Access may also be through state health department sites, libraries and certain practice software

† Other drug bulletins are listed on the International Society of Drug Bulletins website www.isdbweb.org

In my experience, Embase generally includes reference to articles more rapidly than Medline. It also has more drug-related search terms than Medline.

Medline and Embase require some initial understanding to search them appropriately. A tutorial with a librarian or online is advisable before embarking on serious searching. Otherwise searches may be requested via an institutional library or from a local drug information centre.

Information on adverse drug reactions

Clinicians may want to find more information about potential adverse drug reactions. If a particular adverse event is not listed

Table 4

Reviews to assist formulary decision making

Source	Access
In journals such as:	
-P & T Journal	http://ptjournal.com
-PharmacoEconomics	http://adisonline.com
-Formulary	http://formularyjournal.modernmedicine.com
Documents prepared by state therapeutics advisory groups	NSW Therapeutic Advisory Group South Australian Therapeutics Advisory Group Victorian Medicines Advisory Committee Western Australian Therapeutics Advisory Group
The US online resource P & T Community	
Other hospital or organisational bulletins	

in the approved product information, an online search for alerts or warnings, especially from national drug agencies including the TGA, may be useful (see Table 1).

Medicines Safety Update

In Australia, the TGA's Office of Product Review publishes Medicines Safety Update every two months in *Australian Prescriber* and online (at www.tga.gov.au/hp/msu.htm). Summaries relating to adverse event reports are also available on request (by emailing ADR.Reports@tga.gov.au or phoning 1800 044 114).

Table 5

Where to find extensive drug monographs *

Database	Comments
AHFS Drug Information	Highly regarded reference for detailed drug information by generic name. Published by the American Society of Health-System Pharmacists. Easy to navigate. Drugs new to the Australian market may already be included. Includes 'off-label' uses
DRUGDEX (Micromedex)	A well-regarded source of drug information. The monographs are extremely easy to navigate and to find specific sections of information. Includes 'off-label' uses

* Available through many public health departments and hospital and university libraries, otherwise through subscription

Reactions Weekly

The journal Reactions Weekly is useful for finding early reports of adverse reactions. This publication scans the literature and a range of other resources broadly. It also includes news from the World Health Organization Centre for International Drug Monitoring (Uppsala). Titles for articles can be retrieved free online but payment is required for the full text.

Other sources

Local drug information centres may help with a search for adverse event case reports, including reports in the published literature. These centres often have full access to Reactions Weekly. Drug companies may also be consulted. They have mandatory requirements to forward adverse event reports to the appropriate authorities.

Telephone services

Local drug information centre phone numbers can be found on the NPS website (www.nps.org.au/health_professionals/guide_to_medicines_information_resources).

Conclusion

To find useful information about new drugs in a time-efficient manner, it is important to know where valuable information is most likely to be. Understanding how to search online and to make use of resources available through state health department clinical information sites and libraries is fundamental to quick, appropriate drug information retrieval.

Conflict of interest: none declared

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Saxagliptin

Onglyza (Bristol-Myers Squibb)

5 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.3

Incretins help to lower blood glucose after a meal. This effect can be prolonged by inhibiting their metabolism. Sitagliptin and saxagliptin are drugs which do this by inhibiting the enzyme dipeptidyl peptidase 4 (DPP4) (see 'Incretin mimetics and enhancers' Aust Prescr 2008;31:102-8).

Saxagliptin is taken once a day. After absorption, the drug suppresses DPP4 activity for 24 hours. Saxagliptin is metabolised by cytochrome P450 3A4 to a less potent active metabolite. The pharmacokinetics of saxagliptin can therefore be affected by other drugs which act on P450 3A4. For example, inhibition by ketoconazole increases the concentration of saxagliptin and decreases the concentration of its active metabolite. Saxagliptin has a half-life of 2.5 hours and its main metabolite has a half-life of 3.1 hours. The drug and its metabolites are mainly excreted in the urine. It should not be used in patients with moderate or severe renal impairment.

Saxagliptin has been studied as an add-on treatment for patients with type 2 diabetes that had not been controlled by a single drug. It was added to metformin in a placebo-controlled study of 743 patients. After 24 weeks of treatment, the 191 patients who took metformin with saxagliptin 5 mg had a reduction of 0.69% in their concentrations of glycated haemoglobin (HbA1c). There was a rise of 0.13% in the patients who added a placebo to metformin. Saxagliptin also significantly reduced fasting blood glucose.[1]

The relative benefits of increasing the dose of a sulfonylurea or adding saxagliptin were assessed in a study of 768 patients. All the patients were given glibenclamide 7.5 mg daily for four weeks. Patients whose diabetes was not controlled were then randomised to increase the dose to 10 mg daily or add saxagliptin 2.5 or 5 mg. After 24 weeks the mean HbA1c concentration had increased by 0.08% in the glibenclamide group, but decreased by 0.54% in patients who added saxagliptin 2.5 mg and by 0.64% in those who added 5 mg. The combination of treatments had a statistically significantly greater effect on fasting blood glucose than increasing the dose of glibenclamide.[2] The mean reduction from baseline was 0.4 mmol/L with saxagliptin 2.5 mg and 0.5 mmol/L with saxagliptin 5 mg, compared with an increase of 0.04 mmol/L with glibenclamide.

Saxagliptin has also been added to the treatment of patients whose diabetes has not been controlled by a thiazolidinedione. In this study, 565 patients taking pioglitazone or rosiglitazone were randomised to add saxagliptin 2.5 mg, 5 mg or a placebo. After 24 weeks the HbA1c concentration had fallen by 0.66% with 2.5 mg, 0.94% with 5 mg and 0.3% with placebo. The reductions in fasting blood glucose were also significantly greater with saxagliptin.[3]

One study used saxagliptin and metformin in 1306 patients who were starting treatment for the first time. After 24 weeks the combination reduced the concentrations of HbA1c and fasting blood glucose more than either drug alone. Metformin with saxagliptin 5 mg reduced HbA1c by 2.5% compared to 2.0% with metformin and 1.7% with saxagliptin 10 mg alone.[4]

During the trials 3.3% of the patients discontinued saxagliptin 5 mg because of adverse effects compared with 1.8% of the placebo groups. Reasons for stopping treatment included lymphopenia, rashes and increased creatinine concentrations. Hypoglycaemia was reported by 5.2% of patients when saxagliptin 5 mg was added to metformin,[1] 14.6% when added to glibenclamide[2] and 2.7% when added to a thiazolidinedione.[3] In the thiazolidinedione study 8.1% of the patients developed peripheral oedema when saxagliptin 5 mg was added to their treatment.[3]

Saxagliptin's main role is likely to be as an add-on therapy. Its modest efficacy will not bring every patient's diabetes under control. The proportion of patients achieving HbA1c concentrations under 7% after adding saxagliptin 5 mg was 43.5% with metformin,[1] 22.8% with glibenclamide[2] and 41.8% with a thiazolidinedione.[3] Continuing diet and exercise is therefore important. Although saxagliptin has been approved for use with metformin as an initial drug treatment, it is not usual practice to begin treatment with a combination of drugs. As diabetes is a chronic disease, it will be years before the clinical effectiveness and safety of saxagliptin can be confirmed.

T manufacturer provided the AusPAR

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Sertindole

Serdolect (Lundbeck)

4 mg, 12 mg, 16 mg and 20 mg tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2

Sertindole, an atypical antipsychotic drug, was marketed overseas in the 1990s (see 'New antipsychotic medications' Aust Prescr 1999;22:81-3). In 1998 the drug was withdrawn from the European market because of concerns that it could cause fatal arrhythmias. It returned to the market several years later after a review of its safety.

Sertindole blocks dopamine D_2, $alpha_1$ adrenergic and serotonin $5HT_2$ receptors. It has no significant anticholinergic effects and little effect on serum prolactin.

Although sertindole is well absorbed, the absorption is slow. Most of the dose is metabolised and then slowly excreted in the faeces. Severe hepatic impairment is a contraindication. The metabolism involves cytochrome P450 2D6 and 3A so there are potential interactions with drugs such as fluoxetine and erythromycin. Coadministration with inhibitors of P450 3A is contraindicated. The half-life of sertindole varies, because of interindividual variability in metabolism, but averages about three days. While it is suitable for once-daily dosing, there is a delayed onset of action so sertindole is not suitable for emergency treatment of psychosis.

There have been several trials of sertindole and these have been assessed in reviews by the Cochrane Collaboration. The first review included a placebo-controlled study and two comparisons with haloperidol involving a total of 1104 patients with schizophrenia. After 40 days the 54 patients given sertindole 20 mg had improved on a range of rating scales compared to the 48 patients randomised to placebo. The number of patients who needed to be treated for one to be 'very much improved' was approximately eight (confidence interval 4–41, 95% confidence interval). Lower doses were not significantly better than placebo. One of the comparisons with haloperidol only lasted for a few weeks, but the other continued for one year. After eight weeks the scores on the positive and negative symptoms scale (PANSS) were similar for both drugs. Although the mean improvement in the PANSS scores after a year was greater for sertindole, this difference was not statistically significant.[1]

The second review attempted to compare sertindole with other atypical antipsychotics but only included two low quality comparisons with risperidone. These studies involved 508 patients, but only lasted for 12 weeks. There was no clear difference in efficacy.[2]

The extrapyramidal adverse effects of sertindole were similar to those of placebo and less than with haloperidol.[1] Sertindole caused less akathisia and parkinsonism than risperidone, but some of the patients had been given high doses of risperidone.[2]

Both reviews reported on prolongation of the QTc interval on the ECG. More patients taking sertindole had QTc prolongation than those taking placebo, haloperidol or risperidone.[1,2] All patients should have an ECG at baseline before treatment as a prolonged QTc interval is a contraindication. ECG monitoring is mandatory during treatment, particularly around the time of changes in dose. Prolongation of the QTc interval is an indication to reduce or stop treatment. Many drugs can prolong the QTc interval, and they should not be used by patients taking sertindole. In addition to regular monitoring of the ECG, patients need to be checked for hypokalaemia and hypomagnesaemia. These electrolyte disturbances are contraindications to treatment with sertindole.

As sertindole blocks $alpha_1$ adrenergic receptors it can cause postural hypotension. Treatment should therefore begin at a low dose and be increased slowly.

Patients taking sertindole are likely to put on weight. In trials where patients took 24 mg daily for 12 months, 21% gained at least 15% of their baseline weight.

Other adverse effects which occur significantly more often with sertindole than placebo include dizziness, paraesthesia, peripheral oedema and abnormal ejaculation. The safety of sertindole in pregnancy and lactation is uncertain.

Considering the concerns about safety, 8600 patients who had been treated with sertindole were followed up in a company-sponsored study. There were 3819 person-years of exposure with 35 deaths including 11 from cardiac causes and eight suicides.[3] The all-cause mortality rate was 0.92 per 100 person-years of exposure. Cardiovascular and metabolic diseases (including diabetes) were associated with a higher risk of premature cardiac or unexplained death. Sertindole is therefore contraindicated in patients with cardiovascular disease.

An open-label prospective study followed approximately 10 000 patients treated with sertindole or risperidone. Although there

was no significant difference in suicide, cardiac mortality was higher with sertindole. There were 31 deaths from cardiac causes in the sertindole group and 12 in the risperidone group.[4]

Although sertindole has been back on the European market for several years there are many limitations to its use. In view of the safety concerns sertindole should only be used by patients who cannot tolerate or do not respond to other antipsychotic drugs.

[T] manufacturer provided the product information

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The T-score ([T]) is explained in 'New drugs: T-score for transparency' in this issue, Aust Prescr 2011;34:26–7.

* 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 Medicines Agency (www.ema.europa.eu).

[A] At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

Answers to self-test questions

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

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