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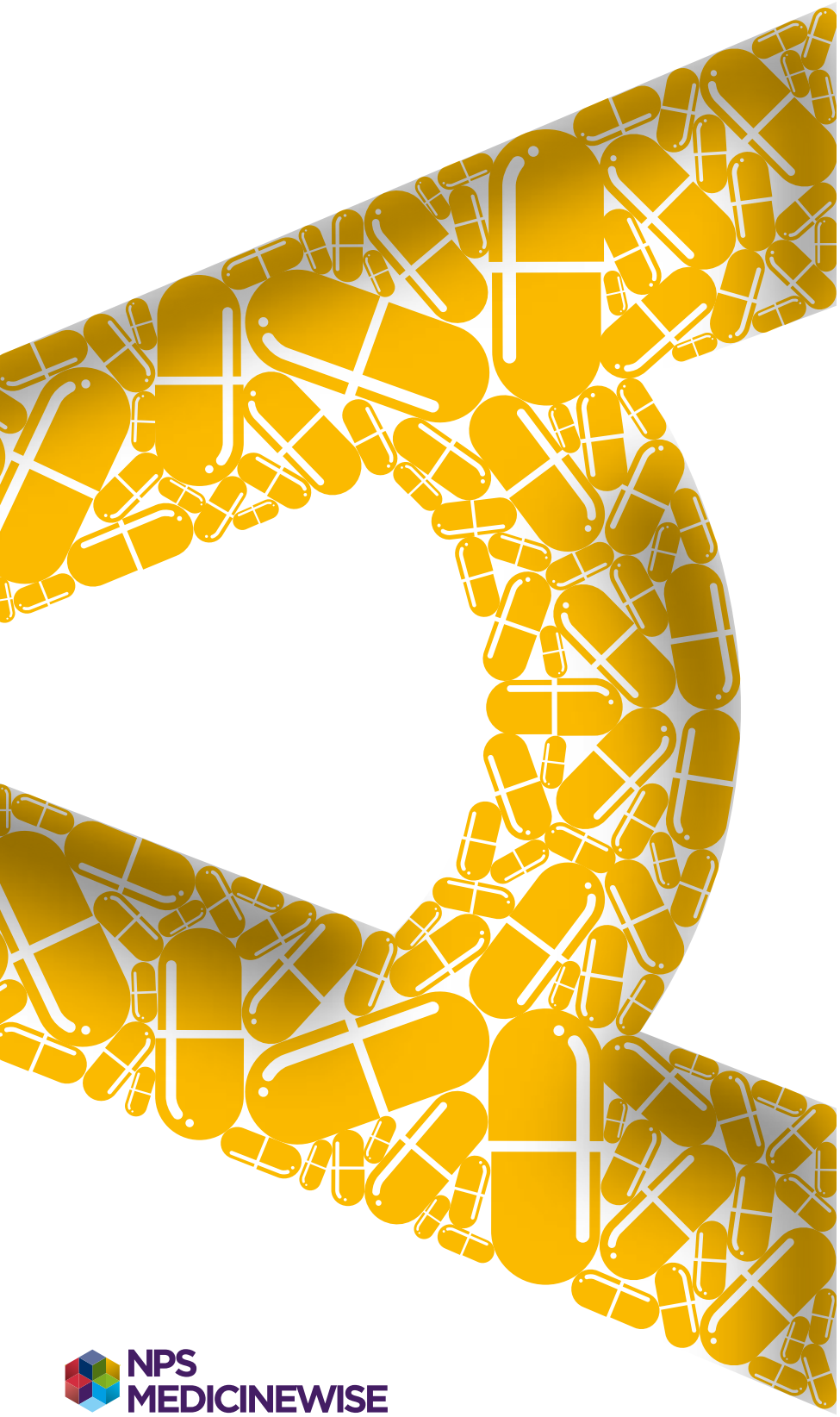

NPS MEDICINEWISE

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EDITORIAL

The seven-year rule for safer prescribing

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Public Citizen's Health Research Group
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Worst Pills, Best Pills News
Washington DC, USA

Key words
adverse effects, drug safety, fluoroquinolones, sibutramine

Aust Prescr 2012;35:138–9

Public Citizen is a national research-based advocacy organisation in the USA. In 1999 our Health Research Group decided to advise against the use of any new prescription drug, except for truly 'breakthrough' drugs, for five years after approval by the Food and Drug Administration (FDA). Our decision was based on the impression that it was during this first post-approval period that a large proportion of drugs either required a new 'black box' warning or were actually withdrawn from the market for safety reasons.[1] This empirical observation was buttressed by the knowledge that the approval process for drugs is heavily tilted toward establishing evidence of benefit, but statistically underpowered to detect all but the most commonly occurring harms. Once the drug is approved, considerably larger numbers of people, including groups which were under-represented in the trials, become exposed to the drug. New adverse reactions and interactions with other drugs are then reported. As the information about harm begins to catch up with the information about benefits, a regulatory decision is frequently needed to either add a new black box warning or to withdraw the drug. The validity of this five-year rule, however, was challenged by the findings of a study published in 2002, based on the ultimate fate of the 548 new drugs approved in the USA between 1975 and 1999.[2]

The study examined how many of the new drugs were eventually the subject of a new black box warning or market withdrawal and when these actions occurred relative to the dates of approval. Our study found that by 25 years after approval, the estimated probability of either acquiring a new black box warning or market withdrawal was 20%. We also found that half of these changes occurred within seven years of the drug's introduction. Of the 16 drug safety withdrawals studied, 94% had occurred within seven years.[2]

Our initial assumption, that five years was a safe enough time to wait after the approval of a non-breakthrough drug before considering its use, turned out to be inadequately conservative. We thus started using a seven-year rule (see Box). Our reasoning was that since one-half of all new safety actions, including almost all safety withdrawals, have occurred within seven years, these drugs should be in a DO NOT USE for seven years category. This change was reflected in the most recent edition of the book Worst Pills, Best Pills[3] and in articles in our monthly publication Worst Pills, Best Pills News.

The Health Research Group's seven-year rule [3]

You should wait at least seven years from the date of release to take any new drug unless it is one of those rare 'breakthrough' drugs that offers you a documented therapeutic advantage over older proven drugs. New drugs are tested in a relatively small number of people before being released, and serious adverse effects or life-threatening drug interactions may not be detected until the new drug has been taken by hundreds of thousands of people. A number of new drugs have been withdrawn within their first seven years after release. Also, warnings about serious new adverse reactions have been added to the labelling of a number of drugs, or new drug interactions have been detected, usually within the first seven years after a drug's release.

The time intervals for bans or new black box warnings would be shorter if the FDA was not infrequently loath, even when faced with strong evidence, to remove unacceptably dangerous drugs from the market or to add new black box warnings in a timely manner. An example is the diet drug sibutramine, for which there was clear evidence of cardiovascular risk at the time of approval in 1997. We petitioned the FDA to ban it in 2002,[4] but it was not removed from the US market until 2010 after further evidence of increased cardiovascular risk emerged. There was also an unwarranted delay in adding a black box warning for all fluoroquinolone antibiotics about the increased risk of tendinitis and tendon rupture. The warning did not occur until after we had petitioned the FDA and later sued the agency.[5]

From the Editor

With summer not too far away, it is an appropriate time (of year) for Jane Hanrahan to review sunscreens. Warmer weather also sees snakes on the move, so Ian Whyte and Nick Buckley report on changes to the way antivenom should be used.

The use of tests to measure bone turnover is the subject of Devika Thomas' article. At present, the tests are not for everyday practice.

Herpes zoster is being increasingly reported in general practice. Michael Wehrhahn and Dominic Dwyer discuss how to prevent it.

Prevention of relapse is also an important part of the management of bipolar disorder. Jon-Paul Khoo considers the current evidence for drug treatment.

In recent years drug regulatory agencies have required drug companies to prepare risk management plans, however these plans are predicated on known risks. The revelation of risks occurs, far too slowly, over time. Better postmarketing surveillance would need to involve more than 10% of adverse drug reactions being reported to the FDA. It would then be sooner rather than later that the required number of adverse reactions occurred to force a change in the product information or the withdrawal of the drug.

Drugs which have been available for more than seven years have already gone through the tests of time and the amount of information about their risks has expanded enormously from what was available when they were initially approved. The worst offenders have either been removed from the market or have important new information about harm that will aid prescribers and patients concerning safer use. As a result, for most patients using older drugs for their approved indications, the benefits will hopefully outweigh the risks.

Conflict of interest: none declared

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Letters to the Editor

Safe prescribing of opioids for persistent non-cancer pain

Editor, – The article by Michael McDonough (Aust Prescr 2012;35:20-4) was well written and includes some good material. However, I consider many statements to be incorrect and dangerous such as:

- 'Every prescription for opioids is fraught with danger'
- 'Before prescribing long-term therapy, there should be a trial period of one month'. By that time many people are already dependent.
- 'If prescribing beyond 12 months a second opinion should be obtained'. This person is dependent.

Donald Beard
Surgeon
Norwood, SA

Michael McDonough, author of the article, comments:

While I find myself agreeing with many of the sentiments expressed in the letter, there is no evidence to support the broader generalisation that after a month or even 12 months many patients are already dependent. However, there is some evidence to support that at least some patients may benefit from extended opioid therapy.[1] Dr Beard is referring to the state of physiological dependence rather than the dependence syndrome as described in DSM IV-TR[2] which is synonymous with the term addiction.

Most people who develop a form of physiological dependence to opioids in the context of medical treatment can be withdrawn from opioids without significant risk of developing persistent craving for opioids or chronic, relapsing and remitting opioid use disorder. Further, there are patients who may derive benefit from continued opioid therapy but within the caveats that both I and others have described.[3]

Having concern about opioid use is always appropriate. However, this concern should not, of itself, justify the absolute avoidance approach, especially in appropriately selected and monitored patients.

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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 Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

LETTERS

Oxycodone and QTc prolongation

Editor, – Thank you to Michael McDonough for his comprehensive article on the safe prescribing of opioids (Aust Prescr 2012;35:20-4). In particular, Table 1 provides useful recommendations for the monitoring and management of possible emerging adverse effects.

The inclusion of oxycodone as a medication which prolongs QTc was surprising. This precaution does not appear in other sources of information discussing oxycodone, such as the reference cited for Table 1[1], the approved product information for oxycodone, the Australian Medicines Handbook[2], Therapeutic Guidelines[3] or the database which records medications that prolong QTc (www.qtdrugs.org). However, there has been research published which supports the occurrence of prolonged QTc by oxycodone in a dose-dependent manner.[4] Is there any other literature that the author can refer us to which supports the prolongation of QTc by oxycodone?

The suggested strategy to manage this potential adverse effect in his article is to recommend an ECG. Given that the prescribing of oxycodone and oxycodone-related deaths have increased in Australia since 2002,[5] does the author, as a practical consideration, advise that in all cases an ECG be performed before the initiation of all formulations of oxycodone?

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Michael McDonough, author of the article, comments:

Thank you for raising two further questions from my article. As you have noted, I was also referring to the article about dose-dependent QTc prolongation by oxycodone.[1]

The concern is that drugs like oxycodone and others yet to be associated with QT prolongation appear to be identified later rather than sooner. We remain uncertain about the precise mechanism of fatal toxicity in both methadone- and more recently the rising number of oxycodone-related deaths in Victoria[2] and the USA.[3] However, the possibility, even if somewhat small, that QT prolongation may be a predisposing factor together with other arrhythmogenic risk factors – such as hypokalaemia, hypomagnesaemia, other drug interactions and heart disease – should be considered.

I believe baseline ECG recording is not appropriate as a screening recommendation because there is no evidence to guide the implementation of such a strategy. Also, this might give rise to concerns about degrees of variation in the QTc interval in various patients and potentially lead to excessive investigation and possibly over-intervention. Consensus recommendations about QTc monitoring in patients on methadone also draw attention to the controversies surrounding the management of degrees of QTc prolongation and the complexities involved in 'risk versus benefit' analyses in this scenario.[4]

I believe an annual ECG recording in the context of long-term and especially high-dose oxycodone treatment would constitute reasonable care and is preferable to not doing so. Furthermore, undertaking an ECG in any patient on oxycodone and with additional risk factors (mentioned above) would no doubt be a more compelling recommendation.

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The importance of medication reconciliation for patients and practitioners

Editor, – I read the timely article by Ms Duguid on medication reconciliation (Aust Prescr 2012;35:15-9) with great interest. Prescribing is a common but often complex and challenging intervention. With a meteoric rise in the ageing population, its attendant polypharmacy and the shift of chronic disease management to primary care, the majority of prescribing will happen in primary care. The peri-discharge period can be perilous. However the article fails to mention some proven strategies in reconciliation such as:

- referring patients for a home medicines review within a stipulated period of discharge (ideally within two days) thereby avoiding rebound admissions and medication misadventures
- engaging a hospital or consultant pharmacist to liaise with the patient's general practitioner, given that managing patients on multiple drugs can be time consuming and require delicate balancing of guidelines and clinical complexities
- checking for potentially inappropriate medicines using Beers Criteria. An Australian version of this list is currently being considered.[1]

With the proliferation of prescribing rights, relevant curricula (medicine, pharmacy and nursing) need to be restructured to explicitly include therapeutics as a formal part of the training. This will build the knowledge and skill base for the quality use of medicines, ideally in an interdisciplinary milieu.

I wish to thank Ms Duguid for highlighting the magnitude of medication-related problems both in individual patients and as a public health issue. I hope there is a strong political commitment to the quality use of medicines which is a central tenet of Australia's National Medicines Policy.

Jay Ramanathan
Physician trainee
Sydney

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Margaret Duguid, author of the article, comments:

I would like to thank Dr Ramanathan for highlighting the risks of medication-related problems occurring following discharge from hospital and the value of hospital and community liaison services and home medicines reviews in the immediate discharge period. Home medicines reviews within 7–10 days of discharge have been shown to decrease the potential for adverse events in at-risk patients discharged home.[1]

To date, timely access to home medicines reviews in the immediate discharge period has been a limitation to their uptake.[2] However, with the ability for general practitioners to refer directly to accredited pharmacists and the proposed hospital home medicines review referral pathway (due to be introduced in late 2012), some of the barriers to early post-discharge medication reviews will be removed.

Patients transferred from hospital to residential aged-care facilities are at particular risk of medication errors. Often their medicines are changed and doses of newly prescribed medicines omitted or delayed. In the case of a resident returning from a hospital admission, ceased medicines were inadvertently administered from a pre-existing medication chart.[3] Checking the medication orders against the medicines list in the discharge summary to identify any discrepancies is an important safety practice. As Dr Ramanathan pointed out, medication reviews early in the admission provide the opportunity to identify and reconcile these discrepancies as well as review those medicines commonly known to cause harm in older patients.

Pharmacists also have an important role in checking the patient's records when new medicines are ordered, ceased or changed and reconciling any discrepancies with the prescriber.

The Australian Commission on Safety and Quality in Health Care has a strong commitment to patient safety. Promoting medication reconciliation is one of its priorities.

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LETTERS

Assessing fever in the returned traveller

Editor, – The article by Anthony Gherardin and Jennifer Sisson (Aust Prescr 2012;35:10-4) provided a good discussion of the issues in this important clinical situation. However, there were several important omissions which I think should be commented upon.

Firstly, measles is a very important cause of fever and rash in the returned traveller, yet this is not mentioned. Many younger Australian doctors will never have seen a case of measles. However, it continues to occur in many resource-poor countries. Measles is one of the most contagious infections known in humans so the importation of even a single case is a public health emergency. It is very important to consider this diagnosis in a returned traveller with fever, respiratory symptoms and a maculopapular (or 'morbilliform') rash. The most rapid and accurate diagnostic test is a polymerase chain reaction on a throat swab or urine, complemented by acute and convalescent serology.

Secondly, in the diagnosis of malaria, rapid antigen tests – immunochromatographic (ICT) card tests – have become standard in nearly all laboratories in Australia, as an addition to the traditional thick and thin blood films. These tests are at least as sensitive as microscopy (by an experienced operator) for malaria caused by *Plasmodium falciparum*, but perform poorly for other species of malaria.

Thirdly, the NS1 antigen test for dengue fever was not mentioned. This test becomes positive earlier than serology and has excellent sensitivity and specificity. Admittedly it is only available in larger laboratories.

Finally, I think the authors have underemphasised the role of the infectious diseases physician. Most infectious diseases departments are very happy to give phone advice and, if necessary, urgent clinical review of any febrile or unwell returned traveller. Furthermore, many of the conditions listed in the article (for example schistosomiasis, yellow fever, trypanosomiasis, leishmaniasis and typhus) are rarely – if ever – seen by general practitioners and should be referred to a specialist regardless of whether or not they are atypical or severe.

Joshua S Davis
Infectious diseases staff specialist
Royal Darwin Hospital

Anthony Gherardin, one of the authors of the article, comments:

We thank Dr Davis for adding to the discussion and would not disagree with anything he has stated. Within the word limit constraints of the article, we could not flesh out too much and the issues raised are very relevant for general practitioners.

Nurturing a close relationship with local infectious disease physicians is also important for safe, high-quality practice.

Undergraduate student prize 2012

Congratulations to Mirjam van den Boom, medical student at the University of Auckland, for winning the Australian and New Zealand Association for Health Professional Educators (ANZAHPE) undergraduate student prize for 2012.

The prize was sponsored by *Australian Prescriber*. It was awarded by the Editor at the ANZAHPE conference in Rotorua in June.

Mirjam's entry topic was 'Supervision of paediatric trainees: effect on patient management and education'.

ARTICLE

Herpes zoster: epidemiology, clinical features, treatment and prevention

SUMMARY

Herpes zoster (also called shingles) is becoming more common as the population ages.

It should be part of the differential diagnosis of a localised unilateral vesicular rash, or a pruritic or painful area before the rash appears.

Early management with antivirals and analgesia is important and may reduce the incidence of postherpetic neuralgia.

Preventing herpes zoster with vaccination is the best way to avoid postherpetic neuralgia and other complications.

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Key words
antivirals, pain, postherpetic neuralgia, shingles, vaccination

Aust Prescr 2012;35:143–7

Introduction

Herpes zoster (from the Greek *herpein* meaning to creep, and *zoster* meaning girdle or belt) is commonly referred to as shingles. It results from reactivation of latent varicella zoster virus in sensory dorsal root or cranial nerve ganglia, and usually manifests as a painful vesicular rash along a dermatomal distribution. In contrast, primary varicella zoster virus infection causes the common childhood illness varicella (chickenpox) which usually manifests as a widespread vesicular rash.

Epidemiology

Varicella zoster virus is highly contagious. One study showed a 75% secondary attack rate with chickenpox in susceptible household contacts.[1] More than 90% of adults have been infected although many will not remember having it or may have had subclinical infection. Therefore, most adults in Australia are at risk of developing herpes zoster.

Studies have shown that about a third of the population will experience herpes zoster during the course of their lifetime with the incidence increasing particularly after the age of 60 years.[2] Recurrent attacks are more common than previously believed, with one study finding a recurrence rate of 4% for men and 7% for women after eight years.[3] The risk of herpes zoster and its complications is greater in immunocompromised people. For example, in a cohort of men who have sex with men, the age-adjusted relative risk of developing herpes zoster was 16.9 in those with HIV and the recurrence rate was 22%.[4] Checking for HIV in at-risk populations who develop herpes zoster is recommended.

While data are conflicting, there is recent evidence of a rise in cases of herpes zoster related to widespread varicella vaccination in children. This has reduced re-exposure to varicella zoster which is needed to boost waning adult T-cell-mediated immunity.

The varicella vaccine for children has been government funded since late 2005 in Australia. In the subsequent three years there was a 2–3% annual increase in herpes zoster dose-specific antiviral use in adults aged 20 and over. Emergency department presentations due to herpes zoster have also increased annually by 2–6%.[5] Similarly, general practitioner data indicate a two-fold rise in herpes zoster cases – from 1.7/1000 consultations in 2000 to 3.4/1000 in 2010.[6] These data support the need for more widespread uptake of the licensed herpes zoster vaccine in adults. Globally there is also evidence that the rate of herpes zoster is increasing.[7] The underlying reasons for this are probably multifactorial and include:

- the ageing of the population
- increased use of immunosuppressant drugs
- widespread childhood vaccination against varicella zoster virus.

Clinical features

Herpes zoster usually begins with a prodrome, such as pain, itching or tingling in the area that becomes affected. This may precede the characteristic rash by days or even weeks but is rarely the only clinical manifestation of varicella zoster virus reactivation (sometimes referred to as *zoster sine herpete*). Typically, patients experience headache, malaise and sometimes photophobia. Abnormal sensation or pain, often described as burning, throbbing or stabbing, occurs in approximately 75% of patients and may be the first noticeable feature. Often pruritus in the affected region is the most prominent feature. Allodynia, or pain induced by light touch, may also be described. Before the onset of the rash and depending on the location, symptoms may mimic pain caused by ischaemic heart disease, cholecystitis or renal colic.

Fig. 1 **Thoracic herpes zoster in a 32-year-old female with HIV**

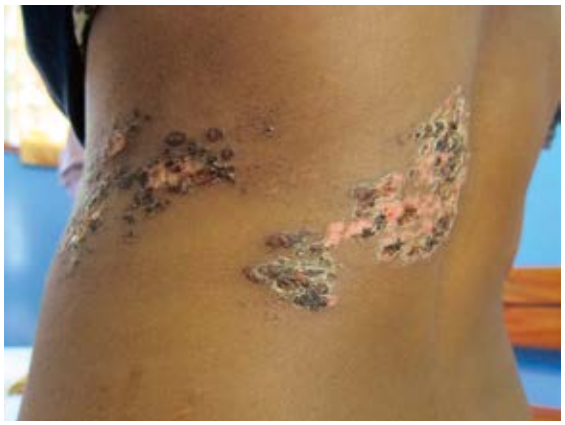
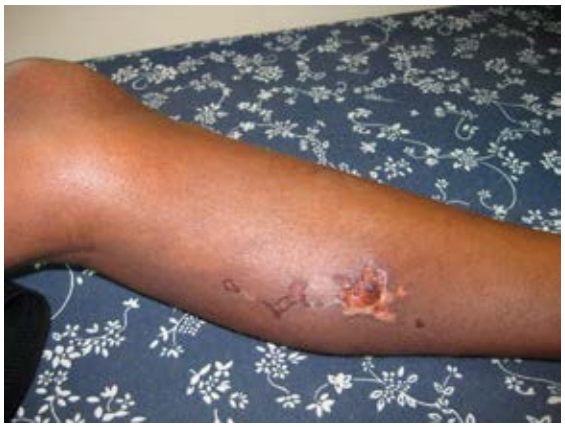


Fig. 2 **Healing herpes zoster in a 30-year-old female with HIV**



Rash

The rash is usually unilateral and may affect adjacent dermatomes, with thoracic, cervical and ophthalmic involvement being the most common. Morphologically it evolves from a maculopapular rash to one comprising clusters of vesicles that ulcerate and crust over the course of 7–10 days (Fig. 1). Healing is usually complete by 2–4 weeks.[8] When all lesions have crusted the rash is considered non-infectious. Residual scarring and pigmentation is common (Fig. 2). Once the characteristic unilateral dermatomal rash of herpes zoster appears, the differential diagnosis includes herpes simplex virus, contact dermatitis, insect bites, folliculitis, impetigo, candidiasis and scabies.[8]

Complications

These occur in a minority of patients and are more frequent in older or immunosuppressed patients.

Postherpetic neuralgia

Postherpetic neuralgia is considered the most common complication and increases with age, affecting up to 30% of people with herpes zoster over the age of 80 years. It is generally defined as pain of at least moderate intensity persisting for three months or longer, although various definitions (and measures of pain severity) have been used in drug trials.[9] It may occasionally last for years. Postherpetic neuralgia is characterised by constant or intermittent, usually severe, burning or lancinating pain that occurs almost daily. Allodynia is present in most cases and can make even wearing clothing an arduous task. Quality of life is invariably reduced. Features that appear to be predictive for the development of postherpetic neuralgia include more severe initial pain, more extensive rash and age over 50 years.[9]

Ocular involvement

Herpes zoster ophthalmicus occurs in 10–25% of cases. This involves the ophthalmic branch of the trigeminal nerve and results in a disproportionately high complication rate (50% in the absence of antiviral drugs) with the eye affected in several possible ways.[8] Keratitis occurs in about two-thirds of cases and conjunctivitis, uveitis, retinitis and glaucoma can all occur. The presence of vesicles on the nose (Hutchinson's sign) due to involvement of the nasociliary branch of the trigeminal nerve has been found to be highly predictive of eye involvement.[2]

Ramsay Hunt syndrome and other neurological syndromes

Less common manifestations of zoster include the Ramsay Hunt syndrome (involvement of the geniculate ganglion of the facial nerve) which manifests as vesicles in the external auditory canal and palate associated with loss of taste to the anterior two-thirds of the tongue and facial weakness.

Rarely, aseptic meningitis, myelitis, peripheral motor neuropathy, cerebellar syndromes, and stroke syndromes due to involvement of cerebral arteries (varicella zoster virus vasculopathy) can occur.

Disseminated zoster

Most individuals with herpes zoster will have some lesions outside the primary dermatome. Disseminated zoster is defined as 20 lesions or more outside the involved dermatome. It tends to occur only in immunocompromised patients and may be associated with visceral involvement (lungs, liver, gut and brain).

Bacterial infections

If bacterial superinfection is suspected, antibiotic treatment to cover *Staphylococcus aureus* and *Streptococcus pyogenes* should be considered, for

example di/flucloxacillin 500 mg every six hours for seven days.

Diagnosis

The diagnosis of herpes zoster is usually clinical, with laboratory tests reserved for more atypical cases. The ideal specimen is a swab from the base of burst new vesicles in viral transport medium. This can be processed for direct fluorescent antibody testing (1–2 hour turnaround time), DNA testing by PCR (turnaround time of one day, but more sensitive especially in older lesions) and viral culture (takes 1–2 weeks and is less sensitive than PCR). Serology for antibodies to varicella zoster virus usually adds little to the diagnosis and may be falsely negative in early presentation due to waning IgG antibodies below detectable levels.

Antivirals

Three oral nucleoside analogues – valaciclovir, famciclovir and aciclovir – are available for the treatment of herpes zoster. They reduce the severity and duration of the illness if started within 72 hours of onset of the rash. However, a Cochrane review concluded that evidence was insufficient to determine if antivirals reduce the incidence of postherpetic neuralgia, depending on the definition of postherpetic neuralgia used.[10] All patients with zoster ophthalmicus should receive antiviral therapy even if it is delayed beyond 72 hours. Similarly, consideration should be given to treating immunocompromised patients or those with disseminated disease.

Current Australian guidelines recommend famciclovir (250 mg three times a day for seven days, or if immunocompromised 500 mg three times a day for ten days) and valaciclovir (1 g three times a day for seven days) as the preferred drugs, given their greater bioavailability and less frequent dosing in comparison to aciclovir.[11] Both the dosage and duration of antiviral treatment are greater for herpes zoster than for herpes simplex. Intravenous aciclovir (10 mg/kg three times a day) is usually reserved for immunocompromised patients with disseminated disease, severe zoster ophthalmicus or central nervous system involvement such as transverse myelitis. Dose adjustment of antivirals in addition to hydration is recommended in renal impairment to prevent nephrotoxicity and neurotoxicity. Viral resistance to the drugs is rare.

Pain management

Treating the pain associated with herpes zoster, particularly in the acute stage, is considered an integral component of management and may have benefits in reducing the severity and incidence of postherpetic neuralgia. This should follow a stepwise approach based on current Australian guidelines.[11] These have been summarised in Table 1. Of note, one double-blind randomised controlled trial showed a reduction in incidence of postherpetic neuralgia at six months by about half with early (within 48 hours of rash onset) commencement of low-dose amitriptyline 25 mg at night (for 90 days) although caution must be used when treating the elderly.[12] Pharmacological management of postherpetic neuralgia follows a similar stepwise approach and may additionally involve the use of gabapentin or pregabalin and topical capsaicin. Transcutaneous electrical nerve stimulation (TENS) may also be useful.[13]

When to refer for specialist assessment

All patients with zoster ophthalmicus should be referred to an ophthalmologist to exclude eye involvement. Those with the Ramsay Hunt syndrome should be seen by an ear, nose and throat specialist. Rare neurological complications such as meningitis or myelitis usually require admission to hospital. Rapid referral to a pain clinic should be considered for patients who have a poor response to initial pain management or those with poorly responding postherpetic neuralgia.[8]

Vaccination

A live attenuated herpes zoster vaccine was effective in decreasing the incidence of herpes zoster by about half and the overall burden of illness by about 60% in

Table 1 **Treatments for acute pain associated with herpes zoster** *

Recommendation	Treatment	Prescribing advice
First-line	Paracetamol: 1 g every 4–6 hours as required, if modified release 1.33 g as required	Maximum 4 g daily
	Prednis(ol)one: 50 mg daily for 7 days then taper over 2 weeks	Use if pain severe Reduces acute pain when given with an antiviral, but has not been shown to reduce postherpetic neuralgia
Other alternatives	Amitriptyline: 10–25 mg at night (maximum dose 75 mg at night)	Response rate of 40–65% Caution in elderly, ischaemic heart disease Nortriptyline less sedating
	Oxycodone: 5 mg every 4 hours as required (maximum 30 mg/day)	Convert to slow release oxycodone/morphine when stable dose achieved Where possible, opioids should be supervised by a pain clinic

* based on eTG[11]

people aged 60 years and over (38 546 people).[14] The vaccine contained the strain used in the childhood varicella zoster virus vaccine, but was at least 14 times more potent. In the vaccine group there was a trend towards a reduction in postherpetic neuralgia cases compared with the placebo group (27/315 (8.6%) vs 80/642 (12.5%) patients). Similarly, a Cochrane review concluded that there was insufficient evidence to determine whether the vaccine was effective in preventing postherpetic neuralgia beyond its effect on reducing herpes zoster.[15]

A large US retrospective cohort study reviewed 75 761 vaccine recipients and found a 55% reduction in herpes zoster (across all age groups) in addition to a 63% reduction in zoster ophthalmicus and a 65% reduction in hospital admissions.[16] More recently, a multicentre study involving 22 439 patients in the 50–59 years age group showed a 70% reduction in herpes zoster.[17]

The zoster virus vaccine has been recommended by the US Advisory Committee for Immunization Practices since 2006 and in Australia[18] since 2009 for those aged 60 years or older. In March 2011 the Food and Drug Administration approved its use in the US in those aged 50–59 years.[17] It can be given to people who have had previous episodes of zoster (although at least one year after the last episode of zoster has been suggested) or in those with underlying chronic conditions. However, it is currently contraindicated in people with significant immune impairment, for example those on high-dose steroids, or patients with HIV who have a CD4+ T-cell count less than 200 cells/microlitre. It is also contraindicated in pregnancy.[8]

The vaccine may be given concurrently with the influenza vaccine, but not within one month of the 23-valent pneumococcal polysaccharide vaccine. It is given subcutaneously and is generally well tolerated. A booster is not currently recommended. Serological testing to elicit varicella zoster virus immune status before or after the vaccine is not necessary. It is not useful for the treatment of acute herpes zoster.[18]

The herpes zoster vaccine should be routinely offered to those 60 years or older and can be considered in those aged 50–59 years. Unfortunately, vaccine availability has been limited in Australia. Reliable supplies are expected in 2013. The vaccine is not currently subsidised.

Preventing transmission

Transmission of varicella zoster virus from a patient with herpes zoster to susceptible contacts is thought to be much lower than with chickenpox although recent evidence of detection of virus in the saliva of a majority of patients with herpes zoster points to a possibly greater risk than previously thought.[19] Preventing such transmission via direct contact and aerosolisation can be done by covering non-crusted lesions with a light non-adherent padding dressing[11,20] after bathing regularly with saline to remove exudate and crusts. Patients should be instructed to avoid susceptible contacts especially those who are pregnant or immunocompromised.

Conclusion

Antivirals are effective in limiting herpes zoster if given within 72 hours of the rash appearing. Pain associated with herpes zoster should be treated early and if a patient responds poorly, they should be referred to a pain specialist promptly.

The zoster vaccine is the best way to prevent herpes zoster and its associated complications such as postherpetic neuralgia.

Professor Dwyer is a member of advisory boards for CSL and MSD.

SELF-TEST QUESTIONS

True or false?

1. Famciclovir reduces the severity and duration of herpes zoster if started 4 days after the appearance of a rash.
2. The zoster virus vaccine reduces disease in people aged 60 and over.

Answers on page 171

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Book review

Australian Don't rush to crush handbook. 1st edition.

Society of Hospital Pharmacists of Australia
Collingwood, Vic: SHPA; 2011.
647 pages
Price: $120 ($110 for members of the SHPA)

This is the first edition of 'Don't rush to crush', by the Society of Hospital Pharmacists of Australia. It is focused on providing a comprehensive selection of Australian-based medication monographs to guide healthcare professionals in the safe administration of medications to people unable to swallow solid oral medicines. It is not designed to replace the approved product information, it is a companion to the clinical decision-making process.

The handbook introduction provides a comprehensive outline of the problems and implications of medication-swallowing difficulties and the alteration of solid oral medications for both general patients and those having enteral feeding. There is a description of the common methods used to alter medications, medications that shouldn't be crushed and a section focusing on the specifics of administering medicines to people with swallowing difficulties or enteral feeding tubes. This section is particularly useful clinically as it contains decision trees and administration flow charts to assist with the practicalities of altering and administering the medications, including preparation details for dispersible tablets, crushed tablets and dispersible capsules.

A great strength of the monographs themselves is their simplicity. Aside from the usual details including generic and brand names, strength and dosage form, a symbol-based quick guide allows the user to easily identify whether a product can be dispersed, crushed, not crushed, is hazardous or cytotoxic, or if it is available as a liquid formulation. For each monograph, specific advice is given for both enteral feeding and general swallowing difficulties.

This handbook would be a valuable resource in all clinical settings including hospital, rehabilitation services, aged care, domiciliary care and general practice. It is practical and comprehensive, and its Australian-based monographs make it the most worthwhile reference source of this kind available and a 'must have' for anyone working with medications.

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ARTICLE

Sunscreens

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Key words
skin cancer, sunburn, ultraviolet light

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SUMMARY

Sunburn is caused by ultraviolet B radiation, but ultraviolet A may be more damaging to the skin. Sunscreens should ideally block both wavebands.

The sun protection factor of a sunscreen is mainly based on blocking ultraviolet B. It does not measure the effectiveness against blocking ultraviolet A.

Sunscreens may be organic or inorganic chemicals. The cosmetic acceptability of metal oxide sunscreens may be improved if they are formulated as nanoparticles.

The absorption of organic sunscreens and nanoparticles does not appear to cause significant systemic effects.

Regular use of sunscreen significantly reduces the development of actinic keratosis, squamous cell carcinoma and melanoma.

Introduction

Sunscreens were originally developed to prevent sunburn from excessive exposure to sunlight. These products were designed to block the ultraviolet B (UVB) rays that cause sunburn but had little effect on ultraviolet A rays (UVA). We now know that UVA causes damage to cells under the dermis which may lead to premature ageing of the skin as well as some types of skin cancers. There are currently sunscreens which block both wavebands. Sunscreens are now used daily by many people and form a component of many 'anti-ageing' moisturising creams, lipsticks and other beauty products.

The solar spectrum and skin damage

Sunlight reaching the earth's surface consists of ultraviolet (290–400 nanometres), visible (400–760 nanometres) and infrared (greater than 760 nanometres) wavelengths. The ultraviolet wavebands are further subdivided into UVB (290–320 nanometres), UVA2 (320–340 nanometres) and UVA1 (340–400 nanometres).

Terrestrial UV radiation consists of 5% UVB which is mostly absorbed by the epidermis and 95% UVA which can penetrate below the dermis (Fig. 1). UVB is higher energy and is responsible for sunburn and direct damage to DNA. More recently identified is the role of lower energy UVA radiation in causing direct[1] and indirect DNA damage by free radical generation, photoageing, immune suppression and photocarcinogenesis.[2]

Sunscreens

Currently there are 33 active ingredients approved by the Therapeutic Goods Administration (TGA) as sunscreens in Australia.[3] These ingredients are divided into organic (consisting of synthetic organic chemicals) and inorganic sunscreens (see Table 1 online with this article at www.australianprescriber.com/magazine/35/5/148/51).

Organic sunscreens

Certain organic chemicals can absorb UV radiation. This radiation provides the energy for a photo-induced tautomerisation or isomerisation of the chemical to a higher energy state. The chemical then returns from the less stable excited state to its original form releasing the excess energy as heat or longer wave, lower energy visible light.[4]

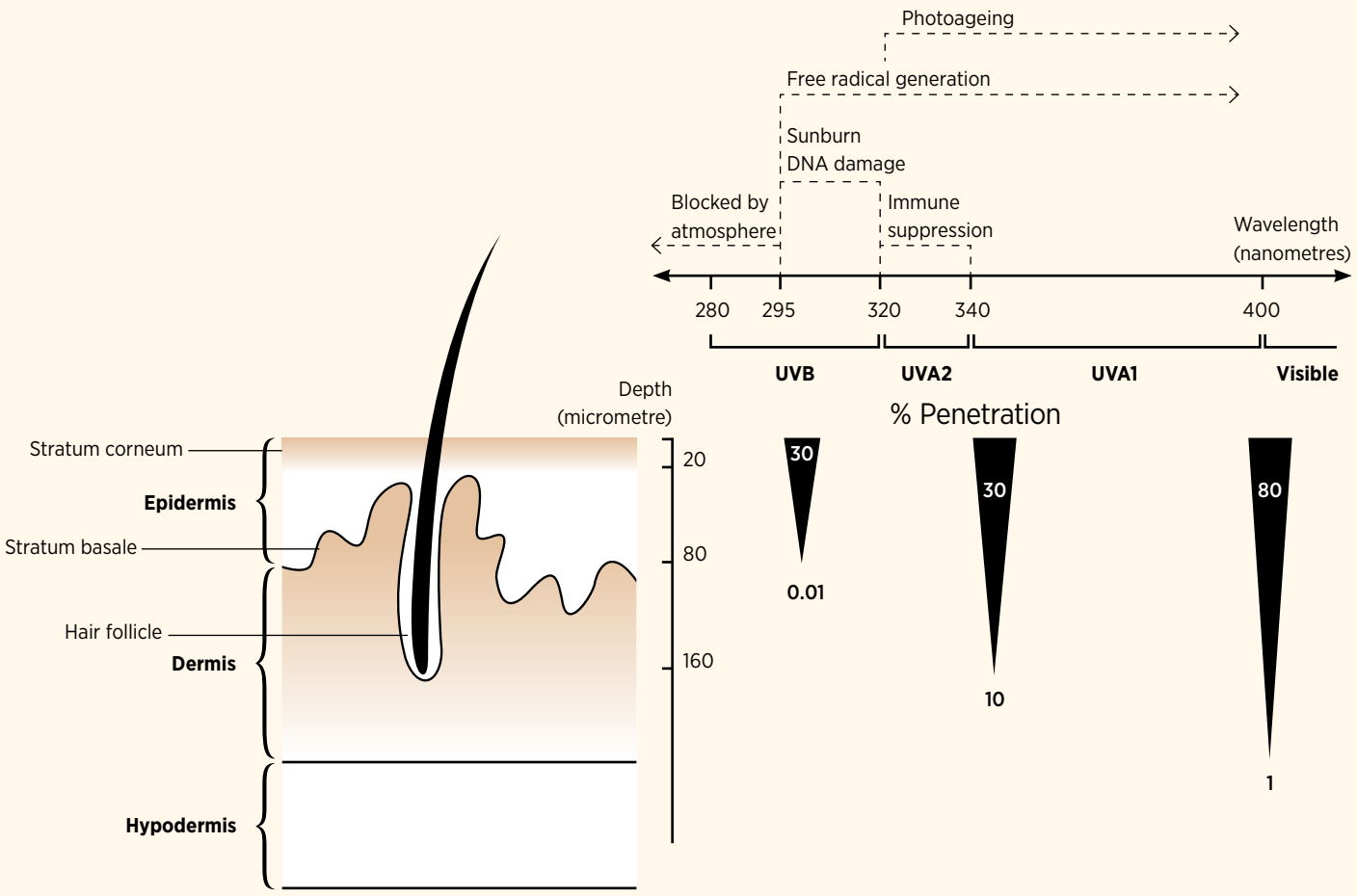
Safety

Most active sunscreen ingredients have been used globally for more than 15–30 years and are considered to be safe in humans. In Australia sunscreens are classified as drugs and all active ingredients undergo stringent approval processes including acute and chronic phototoxicological assessments.

Minor stinging and skin irritations are the most common complaints from sunscreen use. True allergy to sunscreens is uncommon, however adverse reactions from sunscreen use include allergic and irritant contact dermatitis, phototoxic and photoallergic reactions. Sunscreens are becoming one of the most important causes of photoallergy due to their increasing use. Although many suspected sunscreen allergies arise from non-active ingredients in the formulation, the most common sunscreen photoallergens are para-aminobenzoic acid (now rarely used), benzophenones and butyl methoxy dibenzoylmethane.[5]

Concerns have been raised about the oestrogenic effects of some sunscreen ingredients, especially benzophenones, which have a high topical bioavailability, and 4-methylbenzylidene camphor (4-MBC) and octyl methoxycinnamate (OMC), which have shown weak oestrogenic effects in vitro.

Fig. 1 **Schematic cross section of skin showing dermal penetration and biological effects of different wavelengths of UV radiation** *



* modified from reference 2

However, a European review found they did not exert oestrogen-like effects in people, estimating that currently approved sunscreens would need to be 100 000 times more potent before they showed any hormonal effect.[6] Newer ingredients such as ethylhexyl triazone, drometrizole trisiloxane and terephthalylidene dicamphor sulfonic acid have been specifically designed with a high molecular weight to decrease skin penetration, so they are considered safe.[4]

Inorganic metal oxide sunscreens

The metal oxides, zinc oxide (ZnO) and titanium dioxide (TiO_2), were previously referred to as physical sunscreens. Zinc oxide offers true broad spectrum UV protection, although titanium dioxide has better UVB protection. Both oxides have been used in sunscreens for many years, but were originally micro-sized particles (200–500 nanometres) and required a thick application to provide a barrier to reflect and scatter UV rays. This made them cosmetically unacceptable due to the opaque white layer on the skin.

The use of nanoparticles (20–100 nanometres) has improved the cosmetic acceptability of inorganic sunscreens and microfine titanium dioxide has been used in sunscreens since the early 1990s.[7] Microfine or nanoparticles of titanium dioxide and zinc oxide absorb and reflect/scatter UV radiation. They are transparent on the skin.

Safety

Sunscreens containing only inorganic agents have often been recommended for children. However, widespread use of nanoparticles has led to health concerns regarding their safety. There are now some products containing zinc oxide that promote the fact that they do not contain nano-sized particles. In relation to sunscreens, these concerns are focused on whether nanoparticles can penetrate the skin and enter the body and whether nanoparticles generate free radicals.

In 2009, the TGA reviewed the scientific literature about nanoparticles in sunscreens. The vast majority of well-conducted scientific studies found that

during normal use on intact skin nanoparticles do not penetrate below the stratum corneum, but may travel down the hair follicle. However, it is likely that nanoparticles do penetrate through damaged skin.[8]

Titanium dioxide nanoparticles exposed to UV radiation can generate hydroxyl radicals that can damage the DNA of viable cells. However, titanium dioxide nanoparticles in sunscreens are coated with dimethicone or silica to prevent particle agglomeration and these coatings also inhibit free radical generation. The TGA concluded that as nanoparticles do not penetrate into viable skin, concerns relating to systemic toxicity are greatly diminished.[8]

Sun protection ratings

The sun protection factor (SPF) of a sunscreen is determined by a highly regulated clinical test using lamps that simulate solar radiation on human volunteers. It measures the time taken for a minimal erythema to appear when sunscreen is applied compared to the minimal erythemal dose (MED) without sunscreen. An SPF of 15 means that if it takes 10 minutes for skin to start to burn without sunscreen it will take 150 minutes with that sunscreen.

$$\text{SPF} = \frac{\text{MED with sunscreen}}{\text{MED without sunscreen}}$$

The Australian/New Zealand standard 'Sunscreen products – Evaluation and classification' was reviewed in 2011 and the new standard AS/NZS 2604:2012, published in May 2012, permits SPF ratings of 4–50+ (Table 2).[9] The previous edition of the standard permitted SPF ratings of 2–30+.[10] The measurement of SPF uses the biologically relevant endpoint of erythema, however the SPF is biased towards UVB and only measures how effective a sunscreen is at preventing sunburn. It does not measure how effective a sunscreen is at blocking UVA rays.

Previously, the standards for measuring UVA protection were less well defined in Australia.[10] However, the new AS/NZS 2604:2012 aligned the standard for UVA protection with ISO 24443. This requires the monochromatic protection factor at 380 nanometres (MPF380) to be calculated from the in vitro transmission at 380 nanometres. If the SPF is 15 or higher and the SPF/MPF ratio is less than three, then the sunscreen may be identified as broad spectrum.[9]

Sunscreens that have identical SPF ratings will have equal protection against UVB rays under the controlled conditions that are used to determine the SPF. However, the effectiveness of a sunscreen is determined by a number of factors. These include the age of the product and expiry date, the specific ingredients, overall formulation, water resistance, the amount of time that the sunscreen has been exposed to the sun and the amount applied.

The SPF of a sunscreen is measured with a standard application of 2 mg/cm^2 and applying less will not give the same protection.[9] For an average sized adult this means full body coverage requires approximately 30 mL of sunscreen. Current guidelines recommend that to achieve the maximum protection, sunscreen should be applied 20–30 minutes before going outside and then reapplied at least every two hours, especially after swimming. The water resistance of a sunscreen must also be determined using a standardised protocol of repeated 20 minute immersions followed by SPF measurement.[9]

Do sunscreens prevent skin cancer?

The incidence of skin cancers (particularly melanomas) has continued to increase in Australia despite 30 years of 'Slip, slop, slap'. This has been used as an argument against the use of sunscreen.[11] However, it is only since the mid-1990s that broad spectrum sunscreens have been widely available. The use of UVB-only sunscreens may have provided a false sense of security, encouraging people to stay in the sun even longer and therefore increasing their exposure to harmful UVA rays. The long latency between sun exposure and the appearance of skin cancers also means that the efficacy of broad spectrum sunscreens in preventing skin cancer may not become really apparent for another 25 years or more when the population born in the 1990s reach the age when most skin cancers begin to appear.

Table 2 **Current and previous category descriptions for sunscreens** *

Category description	Tested sun protection factor (SPF) (from 2012)	Tested sun protection factor (before 2012)
Very low protection sunscreen	-	2 < 4
Low protection sunscreen	4 < 15	4 < 8
Medium or moderate protection sunscreen	15 < 30†	8 < 15
High protection sunscreen	30 < 50††	15 < 30
	50 < 60††	
Very high protection sunscreen	60 (labelled 50+)††	30+

The sun protection factors are ranges, for example 2 < 4 means at least 2 but less than 4

* The new Australian/New Zealand standard 2604:2012 was published in May 2012

† If the SPF/monochromatic protection factor ratio is less than 3, these sunscreens may be identified as broad spectrum

†† Must also meet broad spectrum requirements

The largest and most comprehensive clinical trial was the five-year randomised controlled Nambour Skin Cancer Prevention Trial. This compared the development of new skin cancers in adults who applied broad spectrum SPF 16 sunscreen daily to face, neck, arms and hands (reapplied if necessary) with a control group who applied sunscreen at their discretion. Follow-up after five and eight years found a significant reduction in the number of precancerous actinic keratoses[11] and squamous cell carcinomas.[12] After 10 years there was a significant reduction in the number of new melanomas.[13] This long-term study clearly shows that regular use of sunscreen can prevent the development of skin cancers. While basal cell carcinomas did decrease, the results were not statistically significant. This may be because basal cell carcinomas result from damage caused early in life and this study only looked at adults.

Sunscreens and vitamin D deficiency

Although vitamin D deficiency is believed to be common in Australia,[14] several prospective clinical or population-based studies have not shown a correlation between vitamin D deficiency and sunscreen use.[15] In Australia, sufficient vitamin D synthesis in healthy active people can usually be gained from 5–15 minutes sun exposure 4–6 times a week (outside the hours of 10 am–2 pm).[14] However, people who may be at risk of vitamin D deficiency should discuss with their doctor sunscreen use, sun exposure and use of vitamin D supplements.

New developments

Recent advances include methods for encapsulating chemical sunscreen ingredients in inert tetraethoxysilane polymers. This microencapsulation improves sunscreen stability, decreases or prevents systemic absorption, increases formulation possibilities and diminishes allergic reactions.[16]

Another approach is the addition of hollow styrene/acrylate polymer beads to the active ingredients. Although the beads do not absorb UV irradiation, they scatter the UV rays increasing the probability of contact with the active ingredients. They work with both organic and inorganic sunscreens to enhance their effectiveness across the whole UV spectrum, making it possible to reduce the amount of active sunscreen ingredients.[17]

Conclusion

Sunscreens have been found to be a safe and effective way of protecting the skin from UV radiation. Despite possible concerns about long-term safety, the benefits outweigh the harms. Sunscreens should only form one part of a sun protection strategy. Staying out of the sun and covering exposed parts of the body with photoprotective clothing remain priorities. If sun exposure cannot be avoided, then the use of a broad spectrum high SPF sunscreen, applied according to directions to protect against sunburn, photoageing and photocarcinogenesis is essential. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. The sun protection factor of a sunscreen is a measure of its effectiveness in blocking ultraviolet A radiation.

4. There is no evidence that the regular use of sunscreen prevents the development of melanoma.

Answers on page 171

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ARTICLE

Antivenom update

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Key words
box jellyfish, envenomation, snake bite, spider bite

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SUMMARY

Recent research has found that one vial of antivenom is sufficient for the treatment of envenomation by all five major groups of Australian snakes.

In snake bite coagulopathy, serial coagulation testing helps determine when patients can be safely discharged, but abnormal results are not an indication for further antivenom.

Clinically significant rhabdomyolysis is more common than previously realised in red-bellied black snake envenomation. Early antivenom administration may prevent rhabdomyolysis, but it is unclear if this benefit outweighs the risk of adverse reactions to antivenom.

Analgesia is the mainstay of treatment for redback spider bite.

Early and effective cardiopulmonary resuscitation is more important than antivenom in box jellyfish envenomation.

Introduction

Antivenoms have been used in Australia since tiger snake antivenom was released for general use by the Commonwealth Serum Laboratories in late 1930.[1] By 1962 all the currently used snake antivenoms (taipan, brown, death adder, Papuan black, sea snake and polyvalent) had been developed. Tick, redback spider and stonefish antivenoms were also available. The last two antivenoms released were for box jellyfish (1970) and funnel-web spider (1980).[1] Despite this long history it is only very recently that the clinical specificity, safety and effectiveness of antivenoms have been critically examined.[2]

Pharmacology

Antivenoms are polyclonal antibody preparations produced from the plasma of animals (usually horses or sheep) which have been repeatedly injected with venoms. They can be whole IgG molecules or processed to create antigen-binding fragments. These polyclonal mixtures contain antibodies of varying titre and affinity to the different toxins in the venom. If venom from just one species is used to immunise the animal then the resulting antivenom is termed 'monovalent'. Polyvalent antivenoms are those taken from animals given multiple different venoms or are made from a mixture of monovalent antivenoms.

Clinical effectiveness should not be assumed

Many snake bites, even from venomous snakes, do not lead to envenomation ('dry bites'). It is recommended to give antivenom only when there is evidence of systemic envenomation (for example coagulopathy, weakness). Further, even though all the antivenoms appear to bind with high affinity to venom and neutralise venom-mediated effects under laboratory conditions, the ability of some antivenoms to reverse or prevent all clinical aspects of envenomation has recently been cast in doubt.[2]

Brown snake

As for other antivenoms, the original recommendation for the initial dose of brown snake antivenom was one vial.[3] This contained enough antivenom to neutralise the venom from a milked snake. However, for many years steadily increasing amounts were given to patients with venom-induced consumptive coagulopathy and the recommended initial doses were increased.[4] Recommendations were being made based on the number of doses of antivenom being given before coagulation returned to normal.

Crucially, there was a failure to consider that recovery from coagulopathy requires resynthesis of clotting factors by the liver. This process usually takes around 12–18 hours. Testing clotting function before this time always returns abnormal results and should not be used to guide repeat antivenom dosing.

Recent studies have confirmed that repeated or larger initial doses of antivenom do not hasten

Fig. 1 **Tiger snake**

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recovery.[5,6] The clinical toxicologists and toxinologists in Australia have therefore returned to the original recommended dose of one vial. Serial coagulation tests should be done to determine when the patient is safe to discharge, not to decide when to give more antivenom.[7]

One vial appears sufficient for most snakes

The Australian Snakebite Project is an ongoing, multicentre, prospective, observational study that recruits patients with suspected snakebite and snake envenomation from over 120 major tertiary and regional hospitals and associated major poisons information centres.[8] Demographic details, clinical effects, laboratory information and treatments are recorded and patients have serial serum samples collected for venom and antivenom quantification. This project has shown that one vial of tiger snake antivenom is sufficient for rough-scaled snake envenomation[8] and one vial of taipan antivenom is sufficient for taipan envenomation.[9] The dose for mulga (king brown) and death adder envenomations has always been one vial.

Red-bellied black snake bite may be undertreated

Red-bellied black snakes were thought to just cause non-specific systemic effects, mild rhabdomyolysis and local effects which could be managed without antivenom.[5] The Australian Snakebite Project found that 95% of patients developed systemic symptoms and there was a previously unrecognised, but clinically significant, myotoxicity. This resulted in longer hospital stays and admission to intensive care units. Myotoxicity did not occur in any patient who received early (within six hours) tiger snake antivenom but occurred in 20% of those who had late or no antivenom.[10] (The use of tiger snake, rather than black snake, antivenom for red-bellied black snake is a long-standing practice which is supported by neutralisation studies but not, as yet, clinical trials.) The implication of this research is that antivenom should perhaps be used more often (and early) in red-bellied black snake envenomation.

In addition, an anticoagulant coagulopathy occurred in the majority (61%) of envenomed patients (although no patients developed life-threatening haemorrhage). An abnormal activated partial thromboplastin time could therefore be used as an early indicator of those patients with systemic envenoming. One vial of tiger snake antivenom should be considered for these patients.[10]

There is a note of caution to be sounded as hypersensitivity reactions occurred in over one-third of all antivenom administrations. This problem is common with tiger snake (as well as death adder and polyvalent) antivenom.[11] An ongoing trial (ACTRN12611000588998) is examining the clinical harm–benefit of using antivenom to treat envenomation by the red-bellied black snake.

Redback spider

The question of efficacy versus effectiveness has also been raised for other Australian antivenoms. Redback spider antivenom has always been recommended for intramuscular injection.[3] However, large molecular weight antibodies would be expected to have very slow systemic absorption after intramuscular injection. An efficacious antivenom would be clinically ineffective if it did not rapidly reach the site of venom action.[2] To test this hypothesis there have been two randomised controlled trials of intravenous versus intramuscular antivenom for redback spider envenoming.[12,13] Both showed no difference in outcome between the routes of administration. In one trial,[13] antivenom concentrations were measured showing that antivenom (as

Analgesia is the mainstay of treatment for redback spider bite

Fig. 2 **Red-bellied black snake**

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Fig. 3 **Redback spider**

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predicted) could only be detected in blood after intravenous administration.[14] As intravenous doses were not more clinically effective, this casts doubt on whether redback antivenom has any clinically meaningful benefit. A placebo-controlled trial of intravenous antivenom (ACTRN12609000063213) is currently underway.

As clinical effectiveness of the antivenom has yet to be demonstrated, adequate analgesia becomes even more important in the management of redback spider bite. Most patients should have an opioid (for example oxycodone 5 mg) plus paracetamol (1 g) and/or a non-steroidal anti-inflammatory drug (for example ibuprofen 800 mg).

Box jellyfish

Box jellyfish antivenom is an example where the difference between in vitro efficacy and clinical effectiveness is extreme. Severe box jellyfish envenoming from *Chironex fleckeri* results in rapidly developing (10–20 minutes) cardiovascular compromise and cardiac arrest. Although the antivenom is widely stocked in northern Australia, there have been at least four deaths despite antivenom administration. Conversely there has been survival after cardiac arrest, without antivenom, when cardiopulmonary resuscitation has been early and effective.[15]

The antivenom is efficacious in that pre-mixing it with venom before injecting the combination prevents cardiovascular collapse in rats.[16] However, the antivenom was not effective in preventing cardiovascular collapse when administered after the venom and was not effective even when the antivenom was infused before the venom.[16] This suggests that the onset of the cardiac toxicity is much more rapid than the binding of antivenom to venom.[2]

Snake antivenoms lack specificity

The horses used to develop the antivenoms are each injected with venoms from all major groups of snakes. Monovalent antivenoms are then formulated to contain sufficient antivenom to neutralise the average amount of venom obtained from milking the snake named on the label. This means that 'monovalent antivenoms' also contain large amounts of antibodies to all families of snakes, regardless of what is stated on the label.[17-19] The exception to this is sea snake antivenom and envenomation. No other monovalent or even polyvalent antivenom provides antibodies raised against sea snake venom and only the specific monovalent antivenom is likely to be useful.[20]

It is preferable to use the correct monovalent antivenom for treatment, but there is some leeway for clinicians. For example, if the type of snake is unknown but the clinical syndrome or geography is most consistent with just one or two snakes, then it is reasonably safe to use monovalent antivenom(s) rather than polyvalent antivenom. Alternatively, if a patient is seriously envenomed by an Australian snake but supplies of the specific monovalent antivenom are not available at that hospital, it is preferable to give the patient whatever monovalent snake antivenom is available rather than delay treatment.

Conclusion

For most Australian snake bites the treatment of envenomation is one vial of antivenom. The antivenom should be appropriate for the family of snakes suspected to have caused the bite.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. The dose of antivenom used to treat a snakebite is determined by the effect of envenomation on coagulation.

6. Patients who develop envenomation after being bitten by a red-bellied black snake can be treated with tiger snake antivenom.

Answers on page 171

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Book review

Community pharmacy: symptoms, diagnosis and treatment. Australia and New Zealand edition. 2nd edition.

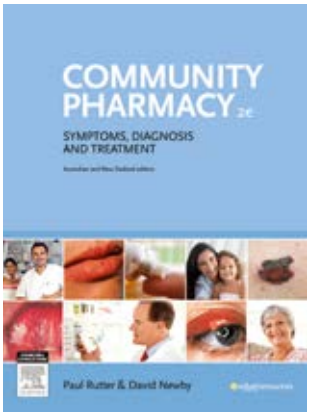
Rutter P, Newby D.
Sydney: Churchill Livingstone Australia; 2011.
360 pages
Price: $115

This is a book on pharmacy primary care written in the context of Australian and New Zealand practice. Topics covered include common respiratory and gastrointestinal disorders, ophthalmology and otic conditions, skin conditions, soft tissue injury, women's health and common conditions affecting paediatrics. There is an introductory chapter on communication skills and patient assessment.

Each chapter is well presented starting with the prevalence, aetiology, signs and symptoms of the conditions, followed by questions to ask in patient assessment, treatment options, contraindications to these treatments, and general self-management advice. There is a reference section at the end of each chapter if you decide to probe further into the topics. This book also has a good chapter on the supply of emergency contraception, motion sickness medications, nicotine replacement therapy, and weight loss products. The authors also incorporate a range of up-to-date evidence for the various treatments from the Cochrane Collaboration, Australian Medicines Handbook, Medicines Safety Update (formerly the ADRAC Bulletin), Therapeutic Guidelines, Food and Drug Administration and from research publications.

Some information is inconsistent with other resources. An example of this is the advice to avoid the use of applicators in the treatment of vaginal thrush in pregnant women even though the Australian Medicines Handbook 2012 states that vaginal applicators may be used with care in pregnancy. Another example is the recommendation on threadworm treatment where all family members of an infected person need to be treated at the same time. The Australian Medicines Handbook states that treatment of other family members is only necessary if infection is not eradicated.

Overall, this book is a great reference in the pharmacy. It could be a useful textbook for pharmacy students if you are after a concise compilation of essential information on a range of primary health conditions manageable in a pharmacy.



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ABNORMAL LABORATORY RESULTS

Bone turnover markers

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Key words
alkaline phosphatase, procollagen peptides, pyridinoline crosslinks, telopeptides

Aust Prescr 2012;35:156–8

SUMMARY

Markers of bone turnover are proteins originating from osteoclast and osteoblast activity or fragments released during the formation or degradation of type I collagen.

Some of these peptides are sufficiently small to be filtered into urine, while larger fragments may be detected in blood.

These markers may provide an assessment of the rate of bone turnover, however they are affected by a variety of physiological and pathological factors.

They cannot be used for screening or the diagnosis of specific diseases.

Introduction

Bone is a dynamic and living tissue and bone remodelling occurs throughout life. The remodelling cycle consists of resorption and formation. Products of the bone remodelling processes are termed bone turnover markers. There are bone formation markers and bone resorption markers. These markers are a quantitative and dynamic reflection of current bone turnover, whereas bone density measurements reflect events that affected bone turnover over the preceding months to years.

Bone remodelling cycle

The bone remodelling cycle begins with the recruitment of osteoclast precursor cells. These differentiate into osteoclasts when they receive signals from osteoblasts. Mature osteoclasts then synthesise and release proteolytic enzymes that digest the collagen matrix. This bone resorption is the first phase of the remodelling cycle. The length of this phase is regulated by apoptosis of osteoclasts. In the next phase of the remodelling cycle preosteoblasts are attracted from mesenchymal stem cells in the bone marrow. Mature osteoblasts synthesise the bone matrix, mainly type I collagen, and regulate the mineralisation of the newly formed bone. Some mature osteoblasts may be trapped within mineralised bone and become osteocytes.

Bone formation markers

Bone formation markers are products of osteoblasts and their activity.

Propeptides of type I procollagen

Type I collagen is part of the bone matrix. Osteoblasts release its precursor, type I procollagen. This undergoes proteolytic cleavage resulting in amino-terminal and carboxy-terminal propeptides of type I collagen (PINP, PICP). The concentrations of PINP and PICP in the circulation are thought to reflect the rate of bone formation. Data from a multicentre trial of teriparatide (parathyroid hormone) versus placebo suggested a relationship between an early rise in PINP and later changes in lumbar spine bone density in the teriparatide treated group.[1]

Alkaline phosphatase

The total serum alkaline phosphatase consists of several isoforms. These isoforms originate from liver, bone, intestine, spleen, kidney and placenta. In healthy adults, about 50% of the serum alkaline phosphatase is considered to be of hepatic origin and the rest is of bone origin. Bone-specific alkaline phosphatase is synthesised in osteoblasts and reflects osteoblast activity during bone formation.

Various physical and chemical methods are used to differentiate liver and bone isoforms in serum. In the absence of liver disease and with other liver enzymes within normal limits, a raised total alkaline phosphatase is considered to represent a rise in bone-specific alkaline phosphatase. Bone-specific alkaline phosphatase is not routinely measured due to the cost.

The concentration of bone-specific alkaline phosphatase is significantly associated with fracture risk regardless of bone mineral density in postmenopausal women.[2] Bone-specific alkaline phosphatase can be used to monitor progress in Paget's disease, although total alkaline phosphatase represents a cheaper and equally valid measure.

Osteocalcin

Osteocalcin is a protein synthesised by osteoblasts which binds to hydroxyapatite in the bone matrix. In addition to its function in regulating bone remodelling via a negative feedback mechanism, it is also an endocrine factor regulating glucose homeostasis. Osteocalcin is unstable once collected therefore testing is not widely offered. While low osteocalcin has been associated with an increased risk of fractures, no significant relationship was seen in prospective trials.

Bone resorption markers

Markers of resorption are type I collagen degradation products. They reflect the rate of bone matrix breakdown and, indirectly, the number of active osteoclasts.

Hydroxyproline is an amino acid found in type I collagen of bone. Urinary excretion rate of hydroxyproline was used in the past to assess bone resorption rate. This assay has been superseded by more specific assays.

Pyridinoline crosslinks

Pyridinoline and deoxypyridinoline are small, cyclic amino structures linking peptide chains of collagen molecules. During resorption these structures are released into the circulation. These small molecules can be detected in urine, where about 40% are bound to various proteins. The urinary concentration of pyridinoline and deoxypyridinoline reflect the rate of collagen degradation.

The fraction bound to protein is not clinically significant, however it is a consideration when various methods of measurement are compared. The concentrations are not generally affected by diet, but are subject to diurnal variation. An early morning sample or a 24-hour urine collection is recommended.

Telopeptides

The N- and C-terminal ends of mature collagen are released during bone resorption and can be detected in the circulation. Although N-terminal telopeptides can be measured in serum, serum concentrations of the C-terminal telopeptide of mature collagen are more useful in monitoring progress in osteoporosis and in bone resorption in multiple myeloma. A raised concentration has been associated with an increased risk of fractures independent of bone mineral density. Measurement may also be useful in monitoring the response to antiresorptive drugs such as bisphosphonates.

Tests for C-terminal telopeptide show high variability within individuals and between individuals. They are affected by marked diurnal variation and food. In addition, concentrations rise with the menopause. It is difficult to determine a reference interval so desirable limits are proposed instead. An early morning fasting blood sample is recommended.

Factors influencing test results

Bone turnover markers are released during normal bone turnover. The concentrations may rise in metabolic bone diseases (for example osteoporosis), other pathological conditions and during physiological processes such as fracture healing and growth spurts. Bone turnover markers are not disease specific. They cannot be used for screening or diagnosis of specific bone diseases. Their concentrations and patterns may be used by specialist units to monitor treatment response and disease progression in several metabolic bone diseases including postmenopausal osteoporosis, corticosteroid-induced osteoporosis and Paget's disease.

Several factors influence the concentration of bone turnover markers in blood or urine including age, sex, fasting or non-fasting, circadian rhythms, menstrual cycle, exercise history and medical history. The interpretation of results is optimised by taking a careful clinical history and collecting specimens under standard conditions.

Bone turnover markers cannot be used for screening or diagnosis of specific bone diseases

Age exerts the greatest effect on bone turnover markers. Concentrations are higher in children and adolescents than in adults. There may be significant increases in markers during growth spurts. In females, bone turnover markers reach a plateau between 20 and 25 years of age, and in males between 25 and 30 years of age reflecting peak bone mass. After the menopause bone turnover increases markedly, as a result of falling oestrogen, and then gradually declines but does not return to premenopausal levels. In contrast, bone turnover decreases in men with ageing.

The intake of food influences bone turnover. Dietary calcium appears to inhibit bone resorption. Calcium supplements taken in the evening significantly reduce resorption markers, in the fasting state, the next morning.

Bone turnover markers have a diurnal rhythm, peaking in the morning. Seasonal variations have been reported. Exercise affects bone turnover markers and immobility results in a marked increase in bone resorption.

Bone turnover markers in clinical practice

Current evidence suggests that bone turnover markers may be useful in some patients with conditions such as osteoporosis,[3,4] for monitoring the response to antiresorptive therapy.[5,6] Intravenous and oral bisphosphonate therapy respectively lead to a decrease in bone resorption markers within days and weeks. The decrease in resorption markers is followed by a decline in bone formation markers. The decrease in bone turnover markers may be sustained for years after cessation of therapy in patients who have been treated for several years.

A significant change in bone turnover markers after starting therapy confirms compliance. A decline

of up to 65% of the baseline bone turnover markers (particularly C-terminal telopeptide) may be expected after potent antiresorptive therapy such as bisphosphonates or denosumab. However, after treatment with oestradiol, the oestrogen analogue raloxifene or strontium ranelate, the fall in C-terminal telopeptide may be less. The magnitude of suppression of baseline bone turnover markers reflects the magnitude of suppression of bone turnover. With oral bisphosphonate treatment, it is not uncommon for the C-terminal telopeptide to fall below 100 nanogram/L. These changes in bone turnover particularly affect bone resorption and have been associated with a rise in bone density.

Osteonecrosis of the jaw

Osteonecrosis of the jaw has been associated with potent antiresorptive therapy such as bisphosphonates and denosumab. The risk following dental extraction may be higher in immunocompromised patients, those with bone metastases and in patients receiving chemotherapy.

The risk of osteonecrosis of the jaw should be determined based on the clinical and drug history. Identification of oversuppression of bone turnover and of those susceptible to osteonecrosis of the jaw may be possible with further experience in bone resorption markers. Currently however, there is insufficient evidence to routinely use bone markers to predict the risk of developing osteonecrosis of the jaw.

Conclusion

Two markers currently used in clinical practice are serum C-terminal telopeptide and amino-terminal propeptide of type I collagen. These markers are dynamic and reflect the resorption and formation rates. However, other analytes such as alkaline phosphatase, parathyroid hormone and 25-hydroxyvitamin D should also be considered. While these markers reflect the rate of bone turnover, they currently have limited clinical utility. They do not predict fracture risk and they are not validated as screening tests in routine clinical practice. Various fracture risk calculators currently available do not include bone turnover markers due to the lack of standardisation of analytical methods and the lack of common reference intervals. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Alkaline phosphatase is not a specific marker for bone turnover.

8. Bone turnover markers can be used to screen for bone diseases.

Answers on page 171

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Dental notes

Bone turnover markers

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Chair

A Goss
Vice Chair

Dental Therapeutics Committee
Australian Dental Association

Bisphosphonate-related osteonecrosis of the jaw is a serious long-standing painful complication of bisphosphonate therapy for benign and malignant bone pathology. It is of particular interest to the dental profession as dental extraction is the most common trigger for the condition.

We note Dr Thomas' careful analysis of the role of bone markers but disagree with her conclusions on the role of C-terminal telopeptide in the management of dental extractions and the less common issue of dental implants for patients with osteoporosis treated by oral bisphosphonates. This disagreement is based on the current literature and Australian studies at the University of Adelaide and South Australia State Pathology.[1]

Firstly, although bisphosphonate-related osteonecrosis of the jaw was initially considered rare, current Australian[2] and international studies[3] confirm the incidence at 1 in 500 to 1500 overall. When extractions are performed in high-risk, older, medically compromised patients the risk is probably of the order of 1 in 200. Given the huge number of patients on oral bisphosphonates worldwide this is a serious health issue.

This is where blood tests may have a role. Although it is agreed that numerous factors alter the values, if C-terminal telopeptide is measured fasted, first thing in the morning, in postmenopausal females over the age of 55, then the standard error of the test is low.

In Australian,[1] US[4] and Israeli[5] studies, all patients with bisphosphonate-related osteonecrosis of the jaw were found to have low bone turnover as measured by C-terminal telopeptide, at the time of onset. When bisphosphonates were ceased the concentration increased and the condition slowly improved. Similarly, the test can be used to monitor 'drug holidays' to take the patient to a higher, safer level of bone turnover. The concentration increases at a rate of 25 pg/mL per month.

In an Adelaide study of over 200 consecutive extractions, C-terminal telopeptide concentrations were found to be of value as a predictor of bisphosphonate-related osteonecrosis of the jaw.[1] Similarly trends are being shown in a much larger study currently being undertaken.

It is agreed that the test will not predict exactly who will develop bisphosphonate-related osteonecrosis of the jaw, but if the concentration is above 200 pg/mL the risk is low and if below 200 pg/mL then the patients are at risk.[4] No clinician relies totally on a single test but a skilled clinician does not disregard a test which might improve the chances of a safer outcome for the patient.

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 3, Number 5, October 2012

In this issue

Post-market vigilance and introduction of the Database of Adverse Event Notifications

The TGA seeks information from a variety of sources, including spontaneous adverse event reports, when monitoring the safety of medicines and vaccines on the market. Information about adverse events (AEs) to medicines that have been reported to the TGA is now available to the public. Health professionals may receive enquiries from patients, who are encouraged to discuss any concerns with a health professional.

Medicine monitoring

When a medicine is first registered and made available in Australia, information about its safety and efficacy is usually only available from clinical trials. Clinical trials provide information about many of the possible risks associated with a medicine, but they do not detect all possible adverse effects, especially rare ones.

Monitoring the safety of medicines contributes to a better understanding of their possible adverse effects when they are used outside the controlled conditions of clinical trials.

The TGA regulatory processes aim to ensure that any risk associated with therapeutic goods is minimised and managed.

Analysis of AEs is one way that the TGA monitors the safety of medicines used in Australia.

Reporting of adverse events

The TGA encourages reporting of all suspected AEs to any medicine available in Australia, including prescription medicines, vaccines, over-the-counter medicines and complementary medicines.

An AE is any untoward medical occurrence in a patient administered a medicine but which does not necessarily have a causal relationship with the medicine. An AE can be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicine, whether or not it is considered to be related to the medicine.

Reporting of AEs complements other sources of safety information. The TGA is particularly interested in serious AEs, such as those that require or prolong hospitalisation; require a visit to the doctor; or result in death, disability, sequelae or birth defects.

It is not mandatory for health professionals to report AEs to medicines. However, the TGA gratefully receives a large number of reports from general practitioners, pharmacists, hospitals and allied health workers. Sponsors, who must report serious AEs, contribute about one-third of the reports.

Most of the states and territories have legislation mandating the reporting of adverse events following immunisation (AEFIs) to their respective health departments, who then report these to the TGA. The TGA encourages health professionals to check legislative requirements for reporting AEFIs with their state or territory health department.

What happens to your reports?

Each report is entered into the national database, which is regularly analysed by TGA staff to identify safety signals. When the TGA identifies a signal, it undertakes

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

a detailed evaluation to establish the possible role of a medicine in causing the AE.

TGA's response to a signal

A response to a signal is a regulatory action that the TGA undertakes to mitigate or minimise the risk identified. Actions could include alteration of product labelling; changes to the Product Information (PI); other changes to conditions of registration; communication of important benefit-risk information to relevant stakeholders; product suspension, cancellation or recall; an investigation of the manufacturing site; or a requirement to undertake a post-market study. Where the signal remains unclear, no regulatory action may be taken and the TGA continues to monitor the medicine.

The Database of Adverse Event Notifications

The TGA recently launched the Database of Adverse Event Notifications (DAEN), an online resource that provides community access to information about AEs to medicines that have been reported to the TGA. The DAEN can be found at www.tga.gov.au/daen.

The DAEN was launched in response to growing public demand for information about medicines and as part of TGA initiatives to be more transparent about its activities. Information in the DAEN is aimed to support the quality use of medicines in Australia and stimulate reporting of AEs.

Information

The DAEN includes AE information on prescription medicines, vaccines, over-the-counter medicines and complementary medicines reported to the TGA from 1971 to up to three months before the date of access. During this three month period, the TGA reviews the reports received and in some circumstances, especially where the report refers to a serious AE, seeks follow-up information from the reporter. The more complete the report is, i.e. where it contains concomitant medications and illnesses, investigations undertaken and timelines, the more useful it is for signal investigations and analyses.

The DAEN does not include information about medicines accessed via the special access, authorised prescriber, clinical trial notification or clinical trial exemption schemes, except where the AE report also includes a suspected general marketed medicine. The data do not include any personal information within the meaning of the *Privacy Act 1988*.

Searching facility

The DAEN provides users with a detailed explanation of the limitations to the data and search results.

There are optional advanced search criteria allowing users to narrow their search to specific AEs or to AEs within broad categories, for example cardiovascular or gastrointestinal disorders.

The DAEN provides users with the ability to view the search results in two formats – a medicine summary and a list of reports. The medicine summary groups reported adverse events together by broad categories. The list of reports provides the details of de-identified case reports.

What the DAEN means for health professionals

Users are advised not to use the database to evaluate the safety of a medicine, as it is not a substitute for medical advice. Users with concerns about their medication are encouraged to consult their doctor or health professional. In these cases health professionals are encouraged to advise patients that a report of an AE does not necessarily indicate there is a causal link between a medicine and an adverse outcome.

The DAEN reflects the TGA's commitment to improve community understanding of its role as a regulator in the health system and to enhance public trust in the safety and quality of therapeutic goods.

The TGA expects that the database will encourage more people to report problems experienced with medicines and so be better able to identify and respond to safety concerns.

Further information

More information, such as PIs and Australian Public Assessment Reports for prescription medicines (AusPARs), is available from the TGA website. When prescribing a new medicine, health professionals are encouraged to discuss the Consumer Medicine Information (CMI) with their patients and focus on the benefits and risks associated with the use of the medicine.

Reporting adverse events

The TGA relies on health professionals, manufacturers and suppliers, as well as consumers to report problems with medicines. This allows the TGA to identify and respond to emerging safety problems. For information on how to report see 'What to report' on page 163 or visit the TGA website.

MEDICINES SAFETY UPDATE

Lenalidomide (Revlimid) and second primary malignancy

The TGA reminds prescribers that lenalidomide (Revlimid) has been associated with an increased incidence of second primary malignancies in clinical trials. Prescribers should consider both the potential benefits and the risk of second primary malignancies, and screen patients for new cancers during treatment.

Lenalidomide is an immunomodulatory agent with anti-angiogenic and antineoplastic properties. In combination with dexamethasone, lenalidomide is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy. Lenalidomide is also indicated for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Evidence of risk with lenalidomide

In clinical trials of previously treated multiple myeloma, an increased incidence of second primary malignancy has been observed in patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to dexamethasone alone (1.38 per 100 patient-years).[1] These were mostly basal cell and squamous cell skin cancers, although solid tumours were also observed.

While lenalidomide is not approved for first-line treatment of multiple myeloma in Australia, in clinical trials of newly diagnosed multiple myeloma, a four-fold increase in the incidence of second primary malignancies has been observed in patients receiving lenalidomide (7.0%) compared to controls (1.8%).[2] These included cases of acute myeloid leukaemia, myelodysplastic syndrome and solid tumours in patients receiving lenalidomide in combination with melphalan or immediately following high-dose melphalan and autologous stem cell transplant. Cases of B-cell malignancies, including Hodgkin's lymphoma, were also observed in the clinical trials, in which patients received lenalidomide in the post-autologous stem cell transplant setting.

Information for health professionals

The following precaution is in the Product Information for lenalidomide:

> Second primary malignancies
>
> Based on a low number of cases, a numerical imbalance in second primary malignancies (comprising mainly of basal cell and squamous cell skin cancers) has been observed in clinical trials in previously treated multiple myeloma patients with lenalidomide/dexamethasone compared with placebo/dexamethasone.
>
> Both the benefit achieved with Revlimid and the risk of second primary malignancies should be considered before initiating treatment with the product. Physicians should also carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as appropriate.

If a decision is made to prescribe lenalidomide, health professionals should screen patients for new cancers during the course of the treatment.

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2. Celgene Corporation. Revlimid (lenalidomide). Health Cananda Product Monograph. Revised 2012.

Erratum: Accidental paracetamol poisoning

The Editor of MSU has become aware of an error in this article published in the August 2012 issue of MSU (vol 3; no 4, 2012). The TGA has referred back to the original source cited in the Lubel et al article in the Medical Journal of Australia in 2007.

The text should read "In a study of 662 patients with acute liver failure, 275 were cases of severe paracetamol-induced hepatotoxicity. 131 (48%) of these 275 cases were the result of an unintentional overdose and 19 (7%) of the 275 patients had not exceeded the recommended maximum daily dose of 4g". The correct reference for this paragraph is:

Larson AM, Polson J, Fontana RF, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-72.

The author and the editor of MSU regret this error.

MEDICINES SAFETY UPDATE

Kogenate: home use Factor VIII and filtration

Kogenate is a recombinant human antihaemophilic Factor VIII which is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital Factor VIII deficiency). It may also be used in patients with Factor VIII inhibitors (neutralising antibodies) who continue to respond to infused Factor VIII.

The use of the correct in-line filtration unit is of particular importance when infusing the reconstituted product. The TGA has been working with the company to update the instructions for reconstitution and administration in the Product Information to reflect the importance of using the filter provided with the product.

Particulate matter derived from incomplete mixing and debris from piercing the seal of the container may be present in the reconstituted product. The use of the filtration unit in the giving set supplied with the Kogenate ensures that any particles are removed from the infusion. The use of the provided giving set also reduces possible treatment failure as a consequence of human coagulation Factor VIII adsorption to the internal surfaces of some alternative infusion equipment.

Supply of Kogenate is through the Haemophiliac Centres, hospitals and individual haematologists. Pharmacists, haemophiliac nurses and medical practitioners are reminded of the importance of using the filtration unit in the giving set supplied with the Kogenate product.

As patients or their carers are responsible for the infusion of Kogenate when it is used prophylactically in the home setting, health professionals are reminded of the need to advise patients and their carers of the importance of using the giving set supplied with the Kogenate, which contains the correct in-line filtration unit.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

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- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
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Medicines Safety Update is written by staff from the Office of Product Review

DISCLAIMER

ARTICLE

Mood stabilisers

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Key words
anticonvulsants, antipsychotics, bipolar disorder, lithium

Aust Prescr 2012;35:164–8

SUMMARY

Many of the drugs used to treat bipolar disorder can be considered to stabilise specific mood phases.

Based on current evidence, lithium and perhaps sodium valproate are the only drugs effective for both acute treatment and the prevention of future episodes.

Quetiapine might also have true mood stabilising properties.

Other anticonvulsants and antipsychotics have evidence to show that they stabilise certain mood states or illness trajectories. They may be used in acute treatment of bipolar disorder, but there is less evidence for their role in maintenance treatment to prevent recurrence.

Introduction

The bipolar disorders are characterised by irregular acute episodes of depression, mania, hypomania and mixed states (various admixtures of elevated and depressed mood). Bipolar disorder is the sixth leading cause of disability worldwide,[1] with a lifetime prevalence of 1–4%.[2] The lifetime risk of death by suicide is as high as 19%.[3] The impact of bipolar disorder on patients' lives is similar to multiple sclerosis, and greater than end-stage renal disease or rheumatoid arthritis.[4] Most of the burden of illness results from depression, low-level symptoms between episodes and comorbidities such as anxiety and substance use.

People with bipolar disorders present commonly to general practitioners. In one primary care study, 9.8% of patients screened positive for bipolar disorder,[5] but only 6.5% were taking mood stabilising treatment. Misdiagnosis is the norm and more than one-third of Australians with bipolar disorder are symptomatic for 10 or more years before diagnosis.[6] Early diagnosis is critical as it allows early intervention. The disorder is almost universally recurrent, so adequate maintenance treatment for prophylaxis should begin during the treatment of the acute episode. All episodes should be treated aggressively to full remission where possible.

What is a mood stabiliser?

Bipolar disorders have different illness phases. To be considered a mood stabiliser, a drug should:

- treat acute depression
- treat acute mania
- prevent depression
- prevent mania.

Some drugs are 'phase-specific treatments'. They work better in some phases than other phases of the illness (Table 1). Most phase-specific treatments are not truly mood stabilising. Current evidence maintains that only drugs such as lithium and perhaps valproate and quetiapine provide acute and long-term illness attenuation, but other anticonvulsants and antipsychotics are also used in treatment.

How mood stabilisers work

There is no specific psychopharmacological mechanism, so how mood stabilisers work is unknown. The possible mechanisms of action of lithium are complex and include:

- altered cell membrane sodium transport
- inhibition of inositol monophosphatase
- reduced protein kinase C activity
- neurogenic/neurotrophic actions
- alterations in serotonin metabolism
- modulation of intracellular signal transduction.[7]

The anticonvulsant drugs used in bipolar disorders may have mechanisms of action which include voltage-sensitive sodium and calcium channels, gamma-aminobutyric acid enhancement, glutamate blockade, or downstream signal transduction cascades.[7]

Atypical antipsychotics are believed to exert a mood stabilising effect through their monoaminergic actions in treating bipolar depression. In psychotic mania they may have dopamine D_2 antagonism or partial agonism and serotonin $5HT_{2a}$ antagonism.[7]

Current evidence

Most of the available treatments (Table 1) perform equally well in the elevated phase of bipolar disorder, and do so relatively quickly. Most available research data are for acute treatment of bipolar mania. This is despite the depressive phase being less amenable to treatment, more frequent and longer lasting. Bipolar

depression causes more suffering and functional impairment and has a greater adverse impact on prognosis.

The selection of drugs is based on their efficacy against the phase, type and stage of bipolar disorder. Comorbidity (physical, psychiatric, substance abuse), tolerability and safety should also be considered.

In practice, effectiveness is limited by poor patient compliance. This is due primarily to tremor, metabolic disturbance, cognitive dysfunction, sedation and yearning for the perceived pleasure of euphoric mood.

Lithium

Despite being discovered 60 years ago, lithium remains the gold standard for mood stabilisation. Lithium has proven efficacy in the treatment of mania, being more effective against classical (euphoric) mania than mixed (dysphoric) variants. It is also moderately effective against the depressive phase. Placebo-controlled trials confirm lithium's prophylactic effect against mania and depression.

Recent meta-analyses[8,9] and longer-term follow-up studies continue to support the preventative efficacy and effectiveness of lithium monotherapy. Lithium also has a specific and strong anti-suicide effect.

Serum lithium concentration is taken as a trough level, 12 hours after a dose for twice-daily dosing, and 24 hours for single-daily dosing. In general, the target range for treating acute phase disturbance should be 0.6–1.2 mmol/L. For maintenance therapy 0.4–0.8 mmol/L will often be adequate. There is a quite large individual variation in the dose required to achieve these targets. The elderly and those with renal impairment usually require lower doses than other patients.

Adverse effects within the therapeutic range are common. Tremor, hypothyroidism, weight gain and sedation are problematic. The most concerning adverse reactions include lithium toxicity, interstitial nephritis, nephrogenic diabetes insipidus and arrhythmia. These occur rarely and adequate monitoring and investigation should allow early intervention.

Serum lithium concentrations can be increased when lithium is co-prescribed with non-steroidal anti-inflammatory drugs, diuretics, ACE inhibitors and metronidazole, risking possible lithium toxicity. Toxicity can also be increased with methyldopa, carbamazepine and calcium channel blockers.

Considering the evidence, and the harm–benefit ratio, lithium is probably underused. Perhaps this is because of perceived difficulties with uptitration, concern regarding rare adverse events or unfamiliarity with the drug. There is also no active marketing for lithium.

Anticonvulsants

Only three anticonvulsants – valproate, lamotrigine and carbamazepine – have any demonstrated mood stabilising effect. The other anticonvulsants do not have the necessary evidence to support their use in treating bipolar disorder. In general, anticonvulsant dosage is determined by clinical effect and tolerability.

Sodium valproate

Valproate appears to be equivalent to lithium against the manic phase,[10] but better against mixed mania.[11] There is only limited evidence of efficacy in depression or maintenance prevention. Meta-analysis shows valproate is superior to placebo for maintenance.[8]

Sedation is often problematic and weight gain is at least as common as with lithium. Hepatotoxicity or pancreatitis can occur rarely. Concern exists regarding whether valproate might be implicated in polycystic ovary syndrome. The teratogenic effects of valproate mean it should not be used by pregnant women or women planning pregnancy.

Valproate concentrations can be increased by fluoxetine, fluvoxamine, topiramate, chlorpromazine, cimetidine, erythromycin and ibuprofen.

Table 1 **Efficacy of drugs used in bipolar disorder**

	Treatment of acute mania	Treatment of acute depression	Mania relapse-prevention	Depression relapse-prevention
Lithium	++	++	++	++
Valproate	++	+	++	+
Carbamazepine	+	0	+	0
Lamotrigine	–	++	+	++
Olanzapine	++	+(+[1])	++	+
Quetiapine	++	++	++	++
Risperidone	++	–	++[2]	–
Ziprasidone	++	–	++	–
Aripiprazole	++	–	++	–
Paliperidone	++	0	0	0
Asenapine	+	0	+	0
Antidepressants	–	–	–	–

++ good double-blind, placebo-controlled evidence
\+ limited supportive double-blind, placebo-controlled evidence
0 no good double-blind, placebo-controlled evidence
– negative studies exist
1 including olanzapine-fluoxetine combination
2 risperidone long-acting injection (depot)

Lamotrigine

Lamotrigine lacks acute antimanic efficacy but has modest antidepressant efficacy as monotherapy or in combination with other drugs. It has prophylactic efficacy against both manic and depressive relapse.

Although lamotrigine is not approved for bipolar disorder in Australia, internationally it is considered a first-line treatment for bipolar depression.[7] Australian clinical practice guidelines support its use in acute bipolar depression and in maintenance prophylaxis.[12]

Lamotrigine is generally well tolerated, with little to no sedation or weight gain.[7] There is a small risk of severe dermatological reactions (Stevens-Johnson syndrome), so patients need slow dose titration. Stop treatment if any rash appears.

Carbamazepine

There is reasonable evidence supporting an antimanic effect of carbamazepine, but lithium, valproate or atypical antipsychotics are often preferred. This is because there are no placebo-controlled data supporting carbamazepine's use in bipolar depression or in the maintenance phase. Furthermore, the adverse effect burden, drug interactions and enzyme induction complicate dosing. Carbamazepine tends to be used only when other treatments have failed.

Antipsychotics

In acute mania, the atypical antipsychotics olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, paliperidone and asenapine have placebo-controlled trials to support them as monotherapies. All but paliperidone have studies which show antimanic equivalence to other mood stabilisers and typical antipsychotics. On meta-analysis, lithium, valproate and antipsychotics are more effective than placebo and have similar effect sizes[13,14] in treating mania. Atypical antipsychotics (olanzapine, quetiapine, risperidone and asenapine) added to mood stabilisers are more effective than mood stabilisers alone in mania. Meta-analysis[14,15] shows a faster and greater response to combination treatment, but at the cost of more adverse effects.

Regarding acute antidepressant effect, the best placebo-controlled evidence is for quetiapine[16,17] and then for olanzapine.[18] No other atypical antipsychotics have evidence of superiority over placebo in treating acute bipolar depression.

Some studies show that atypical antipsychotic drugs (except paliperidone) may protect against relapse, but this is mainly because of their ability to prevent manic episodes. They are less effective in preventing depressive relapse. Atypical antipsychotics demonstrate acute-phase efficacy alone or in combination and assist with relapse prevention when used with mood stabilisers.

Cognitive and metabolic adverse effects (elevations in triglycerides, glucose and cholesterol, appetite increase and weight gain), sedation and somnolence are most problematic. The frequency, severity and extent of these adverse effects varies between treatments. Although they are less frequent than with typical antipsychotics, there may be extrapyramidal adverse effects. Tardive dyskinesia can also occur.

Antidepressants

Antidepressants are not mood stabilising in bipolar disorder. The largest and most rigorous studies of antidepressants in bipolar depression fail to show any benefit.[19] On meta-analysis, there is no evidence of antidepressant efficacy in acute bipolar depression[20] or of relapse prevention over the longer term.[21] Any potential gains need to be weighed against the risks of inducing mood elevation, cycle acceleration and mixed episodes. However, antidepressants remain one of the most prescribed treatments for bipolar disorder and much controversy surrounds their use. Antidepressants are necessary in a proportion of patients, but should only be prescribed with a mood stabiliser, with close monitoring, and should be discontinued sooner than would usually be considered in unipolar depression.

Combination therapy

Patients with bipolar depression, mixed episodes, psychotic features, rapid-cycling and comorbid dysthymia, anxiety or substance use disorders often do not respond, let alone remit, on monotherapy. The vast majority of patients need combination therapy. The combination of lithium and valproate has recently been shown to be superior in maintenance to either drug alone.[22] Clinicians need to be aware of the greater adverse effect burden and potential interactions associated with combination treatment.

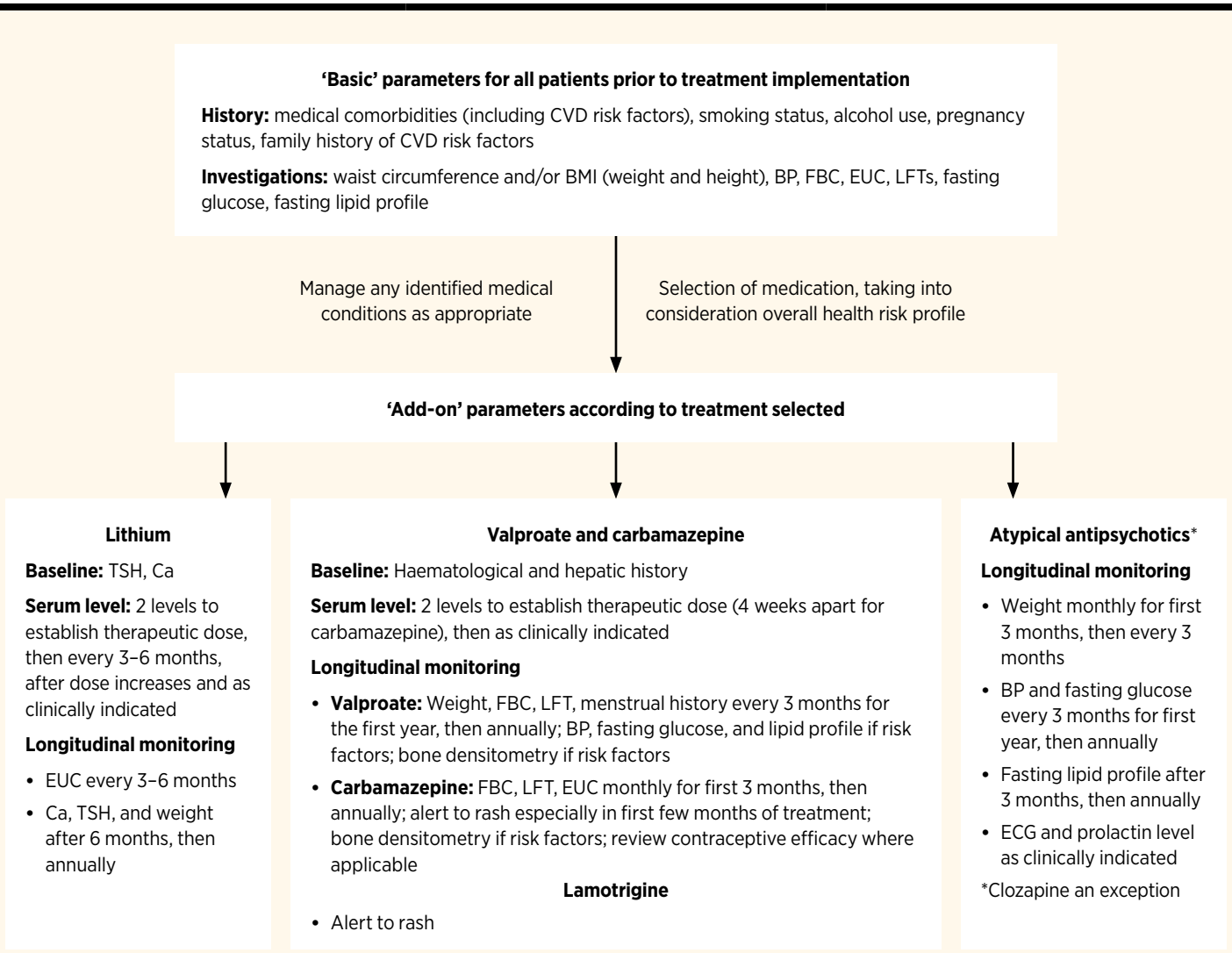
Treatment monitoring

The prescriber needs to ensure that appropriate pre-treatment evaluation, baseline investigations and longitudinal monitoring occur. The International Society for Bipolar Disorders consensus guidelines for safety monitoring[23] are an excellent guide to investigation and monitoring (Fig. 1).

Pregnancy and lactation

Pregnancy and the postpartum are times of increased risk of a bipolar episode. The risks of treatment need to be weighed against the risks to the mother and her child, if there is an untreated episode or mood instability during pregnancy and afterwards.

Fig. 1 **Algorithm for safety monitoring in bipolar disorder** †



CVD	cardiovascular disease	FBC	full blood count	TSH	thyroid stimulating hormone
BMI	body mass index	EUC	electrolytes, urea and creatinine	Ca	calcium
BP	blood pressure	LFT	liver function tests	ECG	electrocardiogram

† Reproduced with permission from the International Society for Bipolar Disorders consensus guidelines for safety monitoring of bipolar disorder treatments[23]

Detailed review, discussion and planning should occur pre-conception, where possible. Although all mood-stabilising treatments can be used during pregnancy, if considered necessary, there are risks of teratogenicity and increased obstetric and neonatal complications.[24] Specialist ongoing care is recommended to monitor medicines during pregnancy and breastfeeding.

Non-pharmacological 'mood stabilisers'

There is a growing body of evidence identifying various non-pharmacological treatments with phase-specific and relapse-prevention efficacy (see Box). These should be used to augment pharmacological strategies where possible.

Non-pharmacological 'mood stabilisers'

- Sleep-wake cycle stabilisation, exercise
- Substance abstinence (illicit drugs, alcohol, nicotine and caffeine)
- Specific psychological interventions (cognitive behavioural therapy, interpersonal-social rhythm therapy, family-focused therapy, mindfulness-based therapies and psychoeducation)
- Non-specific psychosocial interventions (for example, activity scheduling, sleep hygiene, social skills training, therapeutic engagement, supportive therapies, compliance strategies, problem-solving and basic stress management)

Conclusion

Bipolar disorder is a complex and difficult disorder to treat. An awareness of available treatments and their specific benefits and hazards, along with early and accurate diagnosis, will hopefully facilitate better outcomes for those suffering this extremely distressing and disabling chronic illness. Lithium remains the most useful drug for acute treatment and prevention. ≺

Dr Khoo has declared: Honoraria for speaking engagements (AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi-Aventis, Servier, Wyeth); Advisory Board memberships, past and present (AstraZeneca, Eli Lilly, GlaxoSmithKline, Pfizer, Sanofi-Aventis); and educational grants or sponsorships (AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi-Aventis, Servier, Wyeth).

Q:

SELF-TEST QUESTIONS

True or false?

9. When used to treat bipolar disorder, atypical antipsychotics do not cause weight gain.

10. Lithium treatment can cause hypothyroidism in patients with bipolar disorder.

Answers on page 171

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New drugs

Liraglutide

Approved indication: type 2 diabetes

Victoza (Novo Nordisk)

pre-filled multidose disposable pens containing 1.2 mg/3 mL and 1.8 mg/3 mL

Australian Medicines Handbook section 10.1

Glucose in the gut stimulates the release of incretins such as glucagon-like peptide-1 (GLP-1). Incretins are hormones which increase insulin secretion and can be beneficial in diabetes. Like exenatide, liraglutide is a long-acting GLP-1 mimetic produced by DNA recombinant technology. It mimics the action of GLP-1, but, unlike natural incretins, is not rapidly degraded by the enzyme dipeptidyl peptidase 4.

Liraglutide should be prescribed as an adjunct to diet and exercise. It is indicated as an add-on therapy for adults with type 2 diabetes who have insufficient glycaemic control despite maximally tolerated doses of their current drug regimen. Liraglutide can be added to monotherapy with metformin or a sulfonylurea or used as a third treatment in combination with metformin and a sulfonylurea.

The effectiveness of adding liraglutide to other oral hypoglycaemic drugs has been assessed in several randomised controlled trials.[1-6] These were mainly short-term studies (26 weeks) and the primary outcome was the change in mean HbA1c from baseline to the end of the trial.

In one of the open-label trials, 464 patients taking metformin, a sulfonylurea or both were randomised to add liraglutide (1.8 mg a day subcutaneously) or exenatide (10 microgram twice a day subcutaneously). At baseline, mean HbA1c concentrations were 8.1–8.2%. By the end of the trial, average HbA1c concentrations had reduced by 1.12% with liraglutide and 0.79% with exenatide.[1]

In another open-label trial of 665 people already taking metformin (mean baseline HbA1c of 8.5%), adding liraglutide 1.2 mg or 1.8 mg reduced mean HbA1c concentrations by 1.24% and 1.5%. This was compared to sitagliptin (100 mg orally) which reduced HbA1c by 0.9%.[2]

Liraglutide (1.2 or 1.8 mg) has also been compared to rosiglitazone (4 mg) as an add-on to glimepiride monotherapy in a placebo-controlled trial. At the end of the study, mean HbA1c concentrations had decreased by 1.1% with liraglutide (389 people) and 0.4% with rosiglitazone (182 people). HbA1c had increased by 0.2% in patients who added placebo (74 people).[3] In a similarly designed trial, mean HbA1c concentrations were reduced by 1% when liraglutide (1.2 or 1.8 mg) or glimepiride were added to metformin.[4]

In another trial, the higher dose of liraglutide (1.8 mg) was comparable to insulin glargine (titrated dose) when added to combination therapy with metformin and glimepiride. Mean HbA1c concentrations were reduced by 1.33% with liraglutide, 1.09% with insulin and 0.24% with placebo.[5] Mean HbA1c concentrations were also reduced (1.5%) when liraglutide was added to the combination of metformin and rosiglitazone.[6]

In the trials, more people who added liraglutide achieved an HbA1c target of less than 7% than those adding the placebo or the active comparator. Adding liraglutide (1.8 mg) to therapy was also associated with weight loss, however reductions were quite modest ranging from 0.2 to 3.38 kg.[1-6]

The most common adverse effects seen after adding liraglutide to therapy were gastrointestinal. Nausea and diarrhoea occurred in more than 10% of people. Vomiting, constipation, abdominal pain and dyspepsia were also common (1–10%). These adverse events were more likely to occur at the beginning of treatment and usually resolved on continued treatment, however there were withdrawals because of nausea (2.8%) and vomiting (1.5%). Headache, nasopharyngitis and hypoglycaemia were also quite common. Injection-site reactions were experienced by approximately 2% of trial participants, but these reactions were generally mild. A few cases of pancreatitis have been reported during long-term trials (12 months) with liraglutide.

On average, 8.6% of people in the trials developed antibodies to the liraglutide peptide. This has so far not been associated with reduced efficacy.

Liraglutide should be taken once a day by subcutaneous injection in the abdomen, thigh or upper arm. After injection, absorption is slow, with maximum concentrations being reached after 8–12 hours. Its elimination half-life is approximately 13 hours.

Liraglutide should not be used in patients with hepatic impairment (mild–severe) or severe renal impairment (creatinine clearance below 30 mL/minute), including those with end-stage renal disease. There is limited experience in patients with moderate renal impairment and those with congestive heart failure. Liraglutide is not recommended in people with inflammatory bowel disease or diabetic

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 from the manufacturer's approved product information, a drug information centre or some other appropriate source.

gastroparesis. The human GLP-1 receptor is expressed at low levels on thyroid cells, and adverse events such as elevated blood calcitonin, goitres and thyroid cancers have been reported, particularly in patients with a pre-existing thyroid condition. Liraglutide should not be taken during pregnancy and lactation.

Liraglutide delays gastric emptying and may affect the absorption of oral drugs given at the same time. It is not known if it interacts with warfarin so more frequent warfarin monitoring is recommended at the start of liraglutide treatment.

Concomitant use of a sulfonylurea increased the risk of hypoglycaemia in the trials, with more than 10% of patients being affected. More frequent blood glucose monitoring and dose adjustment of the sulfonylurea may be needed. Liraglutide is not recommended with insulin.

Liraglutide reduced HbA1c concentrations when added to oral glycaemic drugs in people with inadequately controlled type 2 diabetes. In short-term trials, its efficacy was similar to adding glimepiride, but was better than adding exenatide, sitagliptin, rosiglitazone or insulin. It is important to remember that HbA1c is only a surrogate marker for efficacy and it is not known if liraglutide will improve the morbidity and mortality associated with type 2 diabetes.

T manufacturer provided the AusPAR

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First published online 13 August 2012

Rifaximin

Approved indication: prevention of recurrent hepatic encephalopathy

Xifaxan (Norgine)

550 mg film-coated tablets

Australian Medicines Handbook section 5.1.10

Patients with chronic liver disease, such as cirrhosis, can develop hepatic encephalopathy. This is a neuropsychiatric syndrome with clinical features ranging from mild cognitive changes to confusion and coma. Hepatic encephalopathy may occur because the liver is unable to clear the ammonia which is produced by intestinal bacteria.

The treatment of hepatic encephalopathy aims to reduce the absorption of ammonia. Typically, lactulose is used as it is cathartic and reduces ammonia production by lowering the gut pH. Rifaximin is a semi-synthetic antibiotic which acts on the intestinal flora. It has been used in the treatment of hepatic encephalopathy,[1] and has now been approved to prevent the recurrence of hepatic encephalopathy.

The tablets are taken twice a day. As the drug is minimally absorbed, most of the dose stays in the gut, but the systemic concentration increases as liver function decreases. There is minimal metabolism, with most of the drug being excreted unchanged in the faeces.

A double-blind trial of rifaximin in prevention involved 299 patients with cirrhosis who were in remission from recurrent hepatic encephalopathy. These patients were randomised to take rifaximin or a placebo for six months or until encephalopathy re-emerged. This occurred in 22.1% of the rifaximin group and 45.9% of the placebo group. Approximately four patients need to be treated for six months to prevent one episode of hepatic encephalopathy. Fewer patients (13.6% vs 22.6%) in the rifaximin group had hospitalisations involving hepatic encephalopathy. Nine patients need to be treated for six months to prevent one admission.[2]

During the trial the adverse events which occurred more frequently with rifaximin than with placebo included peripheral oedema, ascites, anaemia, arthralgia, fever and dizziness.[2] Long-term treatment may lead to the development of resistant bacteria including *Staphylococcus aureus.* Some patients develop *Clostridium difficile* colitis.

The trial did not establish the efficacy of rifaximin as a stand-alone product as more than 90% of the patients were taking lactulose.[2] A previous open-label trial in 140 patients suggested that lactulose alone prevents the recurrence of encephalopathy. After a median

follow-up of 14 months, encephalopathy recurred in 19.6% of the lactulose group and 46.8% of the control group.[3] It therefore seems appropriate that rifaximin is only approved for use when other treatments have failed or are contraindicated.

T T T manufacturer provided clinical evaluation

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First published online 1 August 2012

The T-score (T) is explained in 'New drugs: T-score for transparency', 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)

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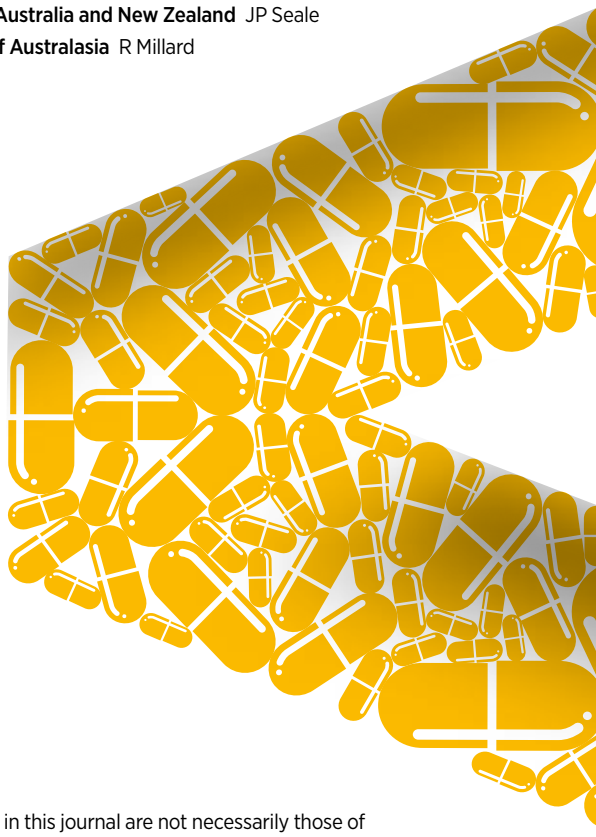

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