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CONTENTS

EDITORIAL

Anaphylaxis and anaesthesia – can treating a cough kill?

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Key words
allergy, cough suppressants, neuromuscular blocking drugs, pholcodine

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In Australia, anaphylaxis during surgery has been estimated to occur in approximately 1 in 10 000 cases. The mortality rate is approximately 4%, with long-term brain injury in an additional 2% of cases.[1] Neuromuscular blocking drugs are responsible for approximately 60% of intraoperative anaphylaxis.[2] Anaphylaxis is twice as likely to occur during surgery when a muscle relaxant is used.[3]

The reported rates of anaphylaxis caused by neuromuscular blocking drugs are much higher in Australia and France[3] than in some other countries.[4,5]

Unfortunately the true incidence of intraoperative anaphylaxis in Australia is unknown. Reporting is voluntary and complicated by the fact that multiple drugs are administered at the time of anaesthesia, making the cause of anaphylaxis unclear. The Therapeutic Goods Administration in Australia received 231 reports between January 2001 and December 2011 citing neuromuscular blocking drugs as a possible cause of anaphylaxis.[6] However, a recent study from Western Australia reporting on the 10-year period 2002 to 2011, found 80 cases of life-threatening anaphylaxis in which neuromuscular blocking drugs were established as the cause of the reaction with subsequent testing.[7] These data, derived from a single state which contained a little over 10% of the Australian population in 2011[8], suggests that anaphylaxis to neuromuscular blocking drugs is under-reported.

The quaternary ammonium ion in neuromuscular blocking drugs is the allergenic portion (epitope). It allows specific binding of immunoglobulin (IgE) to the drug,[9] which can result in IgE-mediated anaphylaxis. However, in up to 50% of cases, anaphylaxis occurs on first exposure to a neuromuscular blocking drug.[5,10] This suggests that there is an alternative source of sensitisation.

Anaphylaxis to neuromuscular blockers in Norway was observed to be approximately 10 times higher than in neighbouring Sweden.[11] An unknown environmental factor containing the quaternary ammonium ion was suspected to be responsible for the difference. Rates of exposure to 84 household chemicals and medicines were found to be similar with the exception of pholcodine, an opioid antitussive. In Norway up to 40% of the population was exposed to this cough mixture, but pholcodine was not available in Sweden.[5] Approximately 6% of Norwegian blood donors had specific IgE antibodies to pholcodine, whereas in Sweden there were no sensitised individuals.[12]

Further studies showed that pholcodine consumption causes production of specific IgE against the quaternary ammonium ion. Without ongoing pholcodine consumption, antibody titres fall to low levels within two years. Re-exposure, however, has a profound booster effect and there is a dramatic rise in pholcodine antibodies in individuals with known previous sensitisation to pholcodine and suxamethonium.[5] Pholcodine was subsequently withdrawn from the Norwegian market by the supplier. Three years after withdrawal, the rate of anaphylactic reactions to neuromuscular blocking drugs in Norway had significantly reduced.[13]

Pholcodine has been used as a cough suppressant since the 1950s. The evidence supporting its efficacy was reviewed by the European Medicines Agency (EMA) in 2011. It commented that 'Being an old product, the methodology used in most efficacy studies with pholcodine would be considered poor by modern standards.'[14]

The only efficacy study in the last 30 years had significant design flaws. It involved only

From the Editor

The misadventures of celebrities regularly highlight the growing problem of misuse of prescription drugs. Malcolm Dobbin reports that deaths involving prescription drugs now exceed those caused by car crashes.

When used appropriately, taking several prescription drugs together can be beneficial. Ruth Webster and Anushka Patel discuss the prospects for polypills in preventing cardiovascular events.

Serious adverse events can result not only from prescription drugs, but also from over-the-counter medicines. Helen Crilly and Michael Rose explore the link between pholcodine cough mixtures and anaphylaxis during surgery. Jerome Sarris reminds us that even herbal medicines – such as those used for mental health – can interact with other drugs.

The prevalence of problem allergies appears to be increasing. It is therefore appropriate for William Smith to assess the role of allergen immunotherapy, including sublingual immunotherapy.

The diagnosis of diabetes is also increasing and Michael d'Emden proposes changing the diagnostic process. Measuring glycated haemoglobin (HbA1c) is a simpler method than the traditional oral glucose tolerance test.

129 patients randomised to receive pholcodine or dextromethorphan, with no placebo arm. Funding for the study came from a manufacturer of pholcodine. Although the conclusion was that 'the efficacy of a three-day course of pholcodine is similar to that of dextromethorphan in the treatment of adult patients with acute, non-productive cough',[15] the EMA said this conclusion was 'non-validated and subjective'.[14] The lack of a control group means that the patients may have had a spontaneous recovery from viral coughs.

A Cochrane review in 2012 of all randomised controlled studies comparing over-the-counter cough suppressant medicines (including dextromethorphan) with a placebo arm in adults and children affected by acute cough included 25 trials. It concluded that 'there is no good evidence for or against the effectiveness of over-the-counter medicines in acute cough'.[16]

So what are the implications of the pholcodine hypothesis for Australia? According to the Australian Register of Therapeutic Goods, pholcodine is found in 58 over-the-counter cough mixtures and lozenges.[17] In Norway there was only one pholcodine-containing product.[5] Any decision to remove or restrict availability of pholcodine in Australia will affect more products and have financial implications for the pharmaceutical industry. A decision to remove or restrict pholcodine must be carefully considered on merit alone, removing financial confounders and keeping the best interests of patients as the central focus.

The TGA has been advised of emerging evidence in this area. It has agreed with the decision of the EMA which concluded that 'the evidence of a link between pholcodine and neuromuscular blocking drug-related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to neuromuscular blocking drugs and subsequent development of anaphylaxis during surgery. Further data need to be generated to clarify the possibility of an association between pholcodine use and neuromuscular blocking drug-related anaphylaxis'.[14]

The evidence linking pholcodine to anaphylaxis due to neuromuscular blocking drugs is compelling, but not yet perfect or complete. In particular, data matching pholcodine consumption and the incidence of reactions by country is hampered by a lack of mandatory reporting systems for anaphylactic reactions throughout the world. Data to establish proof would require a randomised controlled trial of millions of patients. Such a study would be prohibitively expensive. While it may be argued that there is insufficient proof to ban pholcodine, its lack of efficacy and a strong suspicion of danger should be regarded as sufficient for it to be withdrawn.

The adverse outcomes of anaesthetic anaphylaxis – brain injury, permanent disability and death – are significant for the individual and the community. There is good evidence and a plausible mechanism linking pholcodine to an increased risk of anaphylactic reactions to neuromuscular blocking drugs. If pholcodine was being evaluated as a new drug today it is likely that it would not be approved. Furthermore, there are alternative medicines which do not appear to have the same risk of serious harm.

When the arguments are weighed, we believe the over-the-counter availability of products of unproven efficacy cannot be justified when pholcodine has been linked with such a serious complication as anaesthetic anaphylaxis and when alternative treatments exist. Discussions are ongoing with regulatory authorities in Australia and New Zealand. If it is not possible to withdraw pholcodine from the market, we propose a re-classification to 'prescription only'. This would allow medical practitioners to consider the risk of harm before prescribing pholcodine.

Conflict of interest: none declared

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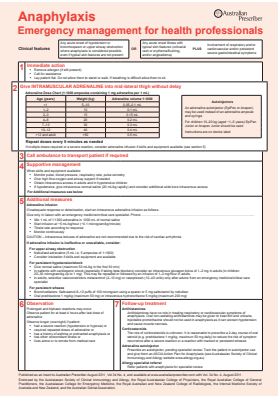

Anaphylaxis

Emergency management for health professionals [wall chart]

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Letters to the Editor

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. When letters are published, they are usually accompanied in the same issue by their responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Conflict of interest

Editor, – Given what we know about the effects of conflicts with the pharmaceutical industry and medical practice, it is simply no longer acceptable to have significant conflicts of interest and provide meaningful information on the benefits and harms of medicines, especially psychiatric medicines. There is a scholarly review of this issue by the co-founder of the Cochrane Collaboration and co-author of the CONSORT guidelines.[1]

Some articles in *Australian Prescriber* are written by authors who have received payments from the pharmaceutical industry. Your publication – and NPS MedicineWise – risks losing its stature if it continues publishing reviews by extensively conflicted authors.

Robert Purssey
Psychiatrist
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The Editorial Executive Committee of Australian Prescriber comments:

The Editorial Executive Committee thanks Dr Purssey for raising the topic of conflict of interest. This topic is of particular importance to organisations that produce independent drug information.[1]

There are several ways that conflict of interest is dealt with in *Australian Prescriber*. All authors and referees are asked to declare any conflicts of interest. The members of the Editorial Committee also have to declare any conflicts of interest and they provide an annual statement of their interests to NPS MedicineWise, the publisher of *Australian Prescriber*.

The Editorial Committee does not automatically reject articles written by authors who declare a conflict of interest. Many clinicians have received support from the pharmaceutical industry to conduct clinical trials. While this may raise the risk of bias, the Editorial Committee believes this can be managed during the editorial process. All articles and editorials are peer-reviewed not only externally, but also by each member of the Editorial Committee. Usually extensive changes are made to articles submitted to *Australian Prescriber*. The Editorial Committee is confident that this process reduces the risk of the published version of a paper being biased by a conflict of interest.

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1. Therapeutic Guidelines. Independent therapeutic advice: how achievable is it? Aust Prescr 2013;36 Suppl 2.

Postoperative pain management

Editor, – I am writing in response to the article by Dr Philip Corke (Aust Prescr 2013;36:202-5) in which he discussed practical issues to consider when prescribing perioperative analgesia. This included planning for longer-term post-discharge pain management in a succinct yet informative manner.

I am disappointed, however, that he did not deal with the disturbing trend of routine prescribing of pregabalin and oxycodone with naloxone controlled-release tablets by acute pain services in certain tertiary hospitals.

Pregabalin is currently listed on the Pharmaceutical Benefits Scheme (PBS) under authority for 'refractory neuropathic pain not controlled by other drugs' and as adjunctive therapy in adults with partial seizures. Dr Corke appears to imply that pregabalin should be used in patients having procedures with a high risk of neuropathic pain, or patients who are predisposed to chronic pain. However, in my personal experience there are many patients who have been started on pregabalin as part of a routine oral analgesic combination after patient-controlled opioid analgesia is stopped. Subsequent management (and cessation) of pregabalin is usually left to the surgical team who do not know why pregabalin was originally prescribed. If the low-risk patient is discharged with pregabalin, then it will perpetuate the myth amongst primary care providers that this drug can be used for chronic pain that is not neuropathic in nature.

There is only one brand of oxycodone in combination with naloxone in Australia. It is PBS-listed for moderate–severe chronic pain unresponsive to non-opioid analgesia. This drug is not considered in recent guidelines.[1] The main incentive to prescribe this drug is to avoid opioid-induced adverse effects, particularly constipation through naloxone as a competitive opioid antagonist at mu receptors in the gut wall. While the oxycodone component is believed to have bioequivalence with other single-drug sustained-release oxycodone, the naloxone component is reported to have less than 3% oral bioavailability due to significant first-pass metabolism, although naloxone, more than oxycodone, appears to be affected more in patients with renal or hepatic impairment.

NPS MedicineWise says that oxycodone with naloxone is 'not indicated for acute pain'.[2] However, the product information suggests otherwise as reproduced here:

> Targin tablets are not recommended for immediate pre-operative use and post-operative use for the first 24 hours after surgery. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual health status of the patient, the exact timing for initiating treatment with Targin tablets depends on a careful risk-benefit assessment for each individual patient.

I have also noticed an increasing trend by several hospital-based acute pain services to prescribe oxycodone with naloxone after patient-controlled analgesia is stopped, even to patients with no history of constipation. Similar to pregabalin, this off-label use is a source of dilemma for surgical teams.

The first submission of oxycodone with naloxone to the Pharmaceutical Benefits Advisory Committee was rejected on the basis of an uncertain and high cost-effectiveness ratio. Subsequent approval was only granted after revised economic modelling comparative with long-term use of oxycodone plus an over-the-counter laxative.[3] Therefore it is uncertain if decision making to prescribe oxycodone with naloxone for postoperative patients with low risk of constipation is based on similarly vigorous harm–benefit assessment.

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Dr Corke, the author of the article, comments:

Thank you for your observations on the postoperative use of pregabalin and oxycodone with naloxone.

Two recent meta-analyses of acute postoperative pain management concluded that pain intensity is not reduced by pregabalin.[1,2] There is a small reduction in 24-hour opioid consumption (10–15 mg). Postoperative vomiting is reduced, but this is only evident if prophylactic antiemetics are omitted.

LETTERS

Patients receiving pregabalin have a greater risk of developing adverse effects (visual disturbance, dizziness, sedation and headache). These effects are predictable given the relatively large doses of pregabalin required (225–300 mg) to achieve an opioid-sparing effect.

On current evidence the routine use of pregabalin for acute pain is not supported. There may however be a role for pregabalin in patients who are receiving high doses of opioids preoperatively or are at risk of severe and prolonged postoperative pain where a neuropathic component is likely, such as post-thoracotomy.[3]

Oxycodone with naloxone may be useful in patients with chronic pain who develop opioid-induced constipation. It is not authorised for use in the management of acute pain. Constipation associated with opioid use in acute postoperative pain is usually managed with concurrent administration of laxatives. Unlike chronic pain, the dynamic nature of acute pain often necessitates breakthrough opioid analgesia, for example during periods of mobilisation and physiotherapy. This is usually managed with the immediate-release oxycodone as needed. In patients receiving oxycodone with naloxone, this additional opioid load may overwhelm the capacity of the naloxone to reduce opioid-induced constipation. Also, patients prescribed oxycodone with naloxone may not receive prophylactic laxatives or may think they are unnecessary and paradoxically may be at a greater risk of developing constipation.

It is likely that the increased use of oxycodone with naloxone by 'certain tertiary hospital' acute pain services relates to its reduced potential for abuse and diversion compared with slow-release oxycodone alone. The naloxone component of the combination will cause withdrawal symptoms when injected and is not favoured by intravenous drug users.[4]

On discharge from hospital, patients and their GPs should receive a written summary of the postoperative pain medications and the planned weaning process. Patients who are discharged on complex analgesics (high-dose opioids and/or gabapentinoids) require review within 4–6 weeks in an acute-on-chronic pain clinic. The surgical team should not be responsible for the postoperative management of complex analgesic pain medications.

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ARTICLE

Pharmaceutical drug misuse in Australia

SUMMARY

The pattern of substance misuse changes over time as the types and availability of illicit and pharmaceutical drugs change.

The number of psychoactive drugs and formulations available in Australia has increased substantially in recent years. Increasing exposure puts individuals at risk of dependence and may escalate use and harm, especially for the more vulnerable such as those with a history of mental health problems or substance abuse disorder.

A new, hidden population dependent on prescribed or over-the-counter medicines is emerging.

The National Pharmaceutical Drug Misuse: Framework for Action has been developed and includes a system to coordinate the safe supply of pharmaceutical drugs subject to misuse.

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Key words
benzodiazepines, codeine, drug-seeking behaviour, opioids, oxycodone, pain

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Introduction

There are many prescription drugs that are misused, including growth hormones and anabolic steroids. However, opioids and benzodiazepines are among the most commonly misused drugs. Apart from those deliberately seeking hedonic drug effects, vulnerable individuals may use substances including psychoactive prescription drugs to make themselves feel better.[1] This new, hidden population[2] may differ from the usual drug user stereotypes and be more highly functioning, have higher socioeconomic status, better education and more social support.

Misuse of prescription opioids

This has become a serious problem in the USA[3] and Canada[4] as the supply of prescription opioids has increased in those countries. There is evidence that a similar problem is developing in Australia. Between 1997 and 2012, oxycodone and fentanyl supply increased 22-fold and 46-fold respectively. Oxycodone is now the seventh leading drug prescribed in general practice. The number of opioid prescriptions subsidised by the Pharmaceutical Benefits Scheme (PBS) increased from 2.4 million in 1992 to 7 million in 2007.

Most people entering Australian alcohol and drug treatment describe unsanctioned use of prescription opioids and benzodiazepines in the preceding four weeks.[5] DirectLine, a Victorian telephone alcohol and drug counselling service, now receives more calls about prescription opioids (31%) than heroin (12%).[6] Many people detained by police test positive for benzodiazepines and prescription opioids.
In needle and syringe programs, the number of people who report that the last drug injected was a pharmaceutical opioid increased from 7% in 2000 to 27% in 2010. Heroin was the main drug injected at the Sydney Medically Supervised Injecting Centre until 2009. Monthly visits for injections of crushed and dissolved prescription opioid tablets (4000) now exceed those for heroin (1200).[7]

Poisons information centres and ambulance data from Victoria report increasing prescription opioid problems. An increasing proportion of patients seeking medically-assisted treatment for opioid dependence nominate pharmaceutical opioids as their primary drug of concern. In the late 1990s, heroin predominated as the cause of hospitalisations due to opioid poisoning, but by 2007–08 prescription opioids accounted for 80% of these admissions. The number of overdose poisoning deaths involving prescription drugs now exceed those from road trauma in Victoria[8] and the USA.[9]

Risks to the community include increased healthcare costs, criminal activity around diversion and trafficking of psychoactive drugs. Pharmaceutical drug crime includes crime to obtain the drugs, and crime resulting from intoxication. Drug seekers may present with fraudulent complaints to multiple doctors and pharmacies without telling each prescriber about the other. Street prices for prescription opioids are similar to those for illicit drugs. Forged prescriptions and identity fraud are used, and armed robbery of pharmacies is a problem. Patients may also share or on-sell their medication.

Opioids

Removal of pethidine from the PBS – because of norpethidine neurotoxicity, misuse liability and self-administration by health practitioners – has limited

drug-seeking for this drug. However, misuse of other pharmaceutical opioids is increasing in parallel with their increasing availability. PBS-subsidised opioids increased from four opioids and 11 preparations in 1992 to eight opioids and 70 formulations in 2007.[10]

Despite large increases in opioid consumption between 1995 and 2007–08, the proportion of adults reporting pain during the last four weeks increased from 57% to 68%, and severe or very severe pain increased from 7% to 10%.[11] Evidence supporting opioid treatment of chronic non-cancer pain is limited, but evidence of serious harm for patients and the community is increasing.

Risks of opioid use

As more people are exposed to prolonged opioid treatment for chronic non-cancer pain, evidence about the harms is increasing. Risks include hyperalgesia, immunosuppression, neuroendocrine dysfunction causing hypogonadism, decreased libido, erectile dysfunction, osteoporosis, increased fracture risk, dental decay and tooth loss due to xerostomia, opioid-related bowel disorder, sedation, cognitive impairment and overdose death.

As many as 36% of patients on opioid therapy meet criteria for lifetime opioid dependence.[12] Childhood opioid poisoning has increased with greater opioid availability in homes and the community.

People taking more than 100 mg morphine or equivalent per day are at greater risk of overdose and death than those on lower doses. However, most people are prescribed low doses and this is where most of the deaths occur. For doses above 100 mg per day, guidelines recommend a review of pain management or referral for specialist advice.

Combination analgesics containing codeine

People dependent on non-prescription over-the-counter analgesics combining codeine with ibuprofen, aspirin or paracetamol may escalate their daily dose to 30–60 or more tablets a day.[13] Harm from high doses of ibuprofen or paracetamol secondary to codeine addiction causes serious morbidity and in some cases death. Practitioners should consider this possibility in patients presenting with the following conditions:

- upper gastrointestinal tract ulcer, haemorrhage and perforation
- non-steroidal anti-inflammatory drug enteropathy with small and large bowel strictures, ulcers mimicking Crohn's disease
- renal tubular acidosis and renal failure
- severe hypokalaemia
- anaemia
- hypoalbuminaemia from protein-losing enteropathy
- liver failure.

Other psychoactive drugs

Benzodiazepines and antipsychotics are also subject to misuse. Moving flunitrazepam to Schedule 8, and removing temazepam capsules from the market because of gangrene from injection of their liquid contents, has eased misuse problems. Now alprazolam has become a particular problem requiring rescheduling to Schedule 8.

Benzodiazepines in combination with other drugs can make overdose from drug toxicity worse. Withdrawal is potentially dangerous, and cessation of prolonged treatment is difficult. In many cases non-drug treatment for insomnia or psychiatric conditions is equally effective and the benefits more enduring than treatment with benzodiazepines.

Quetiapine and olanzapine are also subject to misuse and trafficking, as are dexamphetamine and methylphenidate which are used to treat ADHD.

Response from prescribers and pharmacists

Opioids (except codeine and tramadol) are restricted on the PBS for 'severe disabling pain not responsive to non-narcotic analgesics'. Their use to treat acute pain and cancer pain is well accepted, but there is limited evidence concerning long-term efficacy and safety for chronic non-cancer pain. *Australian Prescriber*,[14,15] NPS MedicineWise,[16] Therapeutic Guidelines[17] and the Hunter Integrated Pain Service[18] provide advice about the use of opioids. Guidance about benzodiazepine prescribing is also available.

Opioid injections are usually contraindicated if the patient can swallow, as the rapid onset of hedonic effect after an injection is highly reinforcing of drug misuse. Pethidine is highly addictive and chronic injection causes myofibrosis.

A cautious approach is warranted given the risks of serious outcomes for the individual and the community. There are numerous guidelines for managing chronic non-cancer pain, back pain, anxiety and insomnia, but they are often not followed.

Information sources for prescribers

A National Pharmaceutical Drug Misuse Framework became available early in 2014.[19] It includes a recommendation for a real-time system to coordinate drug supply, and enable more informed decisions

about the safety of supply of prescription and over-the-counter codeine analgesics with potential for misuse. In the meantime contact the Prescription Shopping Program or the state and territory drugs and poisons contacts (Box).

Box Information about drug-seekers

The Medicare Australia Prescription Shopping Program provides information about people seeking Pharmaceutical Benefits Scheme drugs:
phone 1800 631 181
www.medicareaustralia.gov.au/provider/pbs/prescription-shopping

Contacts for state and territory drugs and poisons units:
www.tga.gov.au/industry/scheduling-st-contacts.htm

Conclusion and recommendation

Treating and assessing pain in patients with a history of substance misuse is high risk and complicated for both patients and their doctors. Referral to a pain or addiction specialist may be needed, particularly if there is a history of substance misuse. Opioid prescribing may be contraindicated, or alternatively, special arrangements and consultation may be required if there is concern about misuse, or examination suggests current injecting drug use.

Supply should only occur after a thorough assessment of need and risk, and in the context of a comprehensive management plan that may include drugs other than those subject to misuse, together with non-drug treatment approaches. ◁

The content and opinions in this article do not necessarily represent the opinions of the organisations with which the author is affiliated.

The author has received honoraria from Pfizer for lectures, which he donated to charity.

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ARTICLE

The 'polypill' in the prevention of cardiovascular disease

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Key words
antihypertensives, aspirin, cholesterol

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SUMMARY

A polypill is a combination of several drugs acting on different risk factors in one formulation. The concept has been proposed as a strategy for reducing cardiovascular events.

Several trials have assessed the efficacy of the polypill compared to placebo for primary prevention. These trials showed short-term risk factor reductions, approximately equivalent to the predicted effects of the individual components. At present, the effect of the polypill on the primary prevention of cardiovascular morbidity and mortality is unknown.

Large trials have been completed comparing a polypill-based strategy with usual care in populations with established indications for the component drugs. These trials have shown improved adherence with a polypill-based strategy.

Introduction

Cardiovascular diseases are the leading cause of premature death and disability globally, despite effective strategies to prevent these conditions.[1] The concept of combining multiple classes of drugs into a single pill to improve accessibility and adherence to preventive therapy for cardiovascular disease has a long history. The term 'asp-olol' was coined for a combination of aspirin and atenolol in the 1970s and patents claiming rights over combinations of various cardiovascular drugs have been filed since the late 1990s.[2-4]

The first major scientific meeting on the concept of a fixed-dose combination pill for preventing cardiovascular disease was held in 2001. The World Health Organization and The Wellcome Trust convened the meeting to discuss evidence-based and affordable interventions for non-communicable diseases.[5] A major impetus for the meeting was the potential for fixed-dose combinations containing aspirin, antihypertensives and cholesterol-lowering drugs (statins) to encourage adherence and reduce the costs of treatment.

The concept of a fixed-dosed combination pill was discussed in a Lancet editorial in 2002[6] and effectiveness and cost-effectiveness analyses were published in the 2002 World Health Report.[7] The term 'polypill' was introduced in 2003[8] when it was suggested that the use of a single pill (containing aspirin, a statin, three antihypertensives and folic acid) in everyone aged over 55 years would reduce cardiovascular disease by more than 80%. The rationale for using three antihypertensive drugs, each at half dose, was to maximise the blood pressure lowering effects, while reducing the risks of adverse effects from any one class of drug.

Clinical trials

Several clinical trials have provided evidence on the feasibility and efficacy of polypills in clinical practice. The polypills used in these trials had different components, however all generally included aspirin, antihypertensives and cholesterol-lowering drugs.

These trials can be broadly grouped into two types:

- comparisons of polypill versus placebo or no treatment – in people with no indications for any of the component drugs, for example people without currently defined hypertension, dyslipidaemia or vascular disease, but who have an above average cardiovascular risk
- polypill versus usual care – in patient populations with indications for **all** the component drugs, for example patients with established coronary disease.

Such trials are crucial to establish the efficacy of cardiovascular polypills and the effectiveness of polypill-based strategies. It is necessary to show that any benefits outweigh the adverse effects of giving a polypill to many people for primary prevention. Using polypills as part of a strategy to improve the appropriate use of medication by patients with established indications for all the components has also raised theoretical concerns that the lack of flexibility associated with fixed combinations may

limit tailoring of individual medications, leading to less optimal control of risk factors. There is also concern that polypills may divert attention from appropriate lifestyle measures to prevent cardiovascular disease.

Polypill versus placebo or no treatment (Table 1)

Several short-term trials have been completed.[9-12] Three trials[10-12] found short-term reductions in risk factors. These were consistent with the expected size of effects (based on published meta-analyses of placebo-controlled trials of antihypertensives and statins) taking into account the baseline risk factors and adherence to treatment. The adverse effects and tolerability of the polypills were consistent with those expected from the individual components.

One study only showed very small risk factor reductions with the polypill compared to placebo.[9] However, imbalances in baseline risk factors suggest the possibility of a flaw in the randomisation process. This study also had low and differential follow-up rates (68% in intervention, 78% in control) so the results should be interpreted with caution.

Three large-scale placebo-controlled clinical trials are underway:

- Prevention of Cardiovascular Disease in Middle-aged and Elderly Iranians Using a Single PolyPill – PolyIran[13]
- Heart Outcomes Prevention Evaluation-3 – HOPE-3[14]
- The International Polycap Study 3 – TIPS-3.[15]

These trials are studying the primary prevention of cardiovascular disease events. The use of polypills in people with an average risk of cardiovascular disease remains contentious, because of ongoing uncertainty over the harm–benefit ratio of the drugs, particularly aspirin. Due to this concern, the HOPE-3 trial has not included aspirin in its polypill, however aspirin is included in the polypill used in the other trials.

The TIPS-3 trial has a 2 x 2 x 2 factorial design (the three components under investigation are the PolyCap, aspirin and vitamin D). It aims to provide some clarity on the harm–benefit ratio of aspirin being included in a primary prevention polypill. TIPS-3 and HOPE-3 are recruiting patients according to age and other risk factors which place them at moderate risk of a cardiovascular disease event over 5–10 years (for example men at least 55 years old with an INTERHEART risk score of at least 10, which is indicative of moderate short-term risk of experiencing a myocardial infarction).[16] The PolyIran study is restricted to people aged 50–79 years.

Polypill versus usual care (Table 2)

The first randomised trial to compare a polypill versus usual care was conducted in Sri Lanka in 216 patients without established disease, but with a 10-year cardiovascular disease risk of at least 20%.[17] This study did not show any significant improvement in adherence, systolic blood pressure or total cholesterol with the polypill. However, the authors of this open-label trial noted that the 'usual care' group received an unusually high level of care following randomisation.

The population in which there is perhaps the least controversy about the potential role of a polypill is patients with established disease, or who are at high risk of cardiovascular disease (at least 15% over five years) and have indications for antihypertensives, cholesterol-lowering and antiplatelet drugs. There are currently four trials, three of which are part of the Single Pill to Avert Cardiovascular Events (SPACE) Collaboration (www.spacecollaboration.org). This is an international group of academic researchers conducting independent, publicly funded, randomised trials. All these studies have used very similar protocols deliberately designed to maximise comparability and to facilitate a meta-analysis of individual patient data.

Initial results from two of the SPACE trials (Use of a Multidrug Pill In Reducing cardiovascular Events – UMPIRE[18] and Kanyini Guidelines Adherence with the Polypill – Kanyini-GAP[19]) have been reported. In both, the polypill-based strategy substantially improved the use of the indicated drugs. In the much larger UMPIRE study this was associated with improvements in blood pressure and cholesterol.[18] The other SPACE trial has completed patient follow-up visits and results are expected later in 2014.[20]

The planned meta-analysis of the three SPACE trials will clarify more precisely the effect of a polypill on the primary outcomes of adherence, systolic blood pressure and total cholesterol. Meta-analysis will also provide the opportunity for looking at subgroups of patients, such as women and the elderly, and primary versus secondary prevention. Results from the meta-analysis will be reported in 2014.

FOCUS is another randomised trial currently underway in Spain, Argentina, Brazil and Paraguay.[21] This trial involves an initial 4000-patient phase aimed at identifying barriers to the implementation of secondary preventive therapies following myocardial infarction. Subsequently, a 1340-patient randomised trial of a polypill versus individual therapies will assess adherence. The results of FOCUS are not expected for several years.

Table 1 **Polypill versus placebo in primary prevention trials** *

Study	Study population characteristics (no previous cardiovascular disease)	Drugs in the polypill (daily dose)	Comparison Number of patients Duration of follow-up	Results		Notes
				Observed mean difference in systolic blood pressure (mmHg)	Observed control-adjusted reduction in low density lipoprotein (mmol/L)	
Malekzadeh et al 2010[9]	Inclusion criteria: >50/55 years, no previous cardiovascular disease; not on active blood pressure or lipid lowering drugs. No exclusion for diabetes	aspirin (81 mg) enalapril (2.5 mg) atorvastatin (20 mg) hydrochlorothiazide (12.5 mg)	placebo n=475 12 months	2.4	0.45	Imbalance in baseline characteristics suggests possible inadequacy of randomisation Differential follow-up rate: 68% in intervention, 78% in control
Pill Collaborative 2011[10]	Inclusion criteria: five-year cardiovascular disease risk >7.5% (based on Framingham risk score) or 5–7.5% and two cardiovascular disease risk factors. No exclusion for diabetes	aspirin (75 mg) lisinopril (10 mg) hydrochlorothiazide (12.5 mg) simvastatin (20 mg)	placebo n=378 12 weeks	9.9	0.75	99% follow-up
Wald 2012[11]	Inclusion criteria: over 50 years of age	amlodipine (2.5 mg) losartan (25 mg) hydrochlorothiazide (12.5 mg) simvastatin (40 mg)	placebo n=86 12 weeks (cross-over randomised control trial)	17.9	1.4	98% follow-up
The Indian Polycap Study 'TIPS' 2009[12]	Inclusion criteria: at least one cardiovascular risk factor (including diabetes)	hydrochlorothiazide (12.5 mg) atenolol (50 mg) ramipril (5 mg) simvastatin (20 mg) aspirin (100 mg)	Multi-armed study with arms not taking various classes of drugs used as comparator n=2053 12 weeks multi-armed study (some 8–12 weeks)	7.4	0.72	85% follow-up

* adapted from Elley, 2012[22]

Table 2 **Polypill versus usual care trials**

Study (location)	Study population characteristics	Drugs in the polypill (daily dose)	Number of patients	Duration of follow-up	Outcomes being studied	Results
Sri Lanka Polypill study[17] (Sri Lanka)	≥50 years old if female and ≥40 years old if male 10-year total cardiovascular disease risk score ≥20%	RHP Version 2b: aspirin 75 mg simvastatin 20 mg lisinopril 10 mg hydrochlorothiazide 12.5 mg	216	3 months	systolic blood pressure, total cholesterol, 10-year cardiovascular disease risk	No significant difference in systolic blood pressure, total cholesterol
UMPIRE[18] (UK, Ireland, Netherlands, India)	Established cardiovascular disease or cardiovascular disease risk of >15% over 5 years	RHP version 1c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg RHP version 2c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg	2004	minimum 12 months	adherence, systolic blood pressure, total cholesterol	Significant improvement in adherence, systolic blood pressure and low density lipoprotein cholesterol
Kanyini-GAP[19] (Australia)	Established cardiovascular disease or cardiovascular disease risk of >15% over 5 years	RHP version 1c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg RHP version 2c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg	623	minimum 12 months	adherence, systolic blood pressure, total cholesterol	Significant improvement in adherence
IMPACT[20] (New Zealand)	Established cardiovascular disease or cardiovascular disease risk of >15% over 5 years	RHP version 1c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg atenolol 50 mg RHP version 2c: aspirin 75 mg lisinopril 10 mg simvastatin 40 mg hydrochlorothiazide 12.5 mg	513	minimum 12 months	adherence, systolic blood pressure, low density lipoprotein cholesterol	2014
FOCUS[21] (Argentina, France, Italy, Spain, Switzerland)	Postmyocardial infarction	aspirin 100 mg simvastatin 40 mg ramipril (2.5, 5, 10 mg)	Phase 1 – 4000 Phase 2 – 1340	9 months	adherence, blood pressure, low density lipoprotein cholesterol, safety, cost-effectiveness	Uncertain publication date

RHP Red Heart Pill

Polypills in practice – where are we now?

Despite several polypills that simultaneously address more than one risk factor having been evaluated over the past decade, few have been marketed in high income countries such as Australia.[24] The exception is a combination of amlodipine besylate and atorvastatin calcium which has been available for some time, with over a million scripts written per year in Australia.[23] However, no polypills containing statins, multiple blood pressure lowering drugs or aspirin are currently available. The polypill used in the FOCUS trial has been licensed in Guatemala, and several other polypills are available in India including the polypill used in the TIPS series of clinical trials.

The regulatory pathway for polypills is currently challenging. To support an indication for prevention of cardiovascular disease in individuals without any current indications for treatment, placebo-controlled clinical trials with morbidity and mortality outcomes will be required. For use in patients with established indications for the component drugs of a polypill, complex pharmacodynamic and pharmacokinetic testing to demonstrate equivalence will be required. However, for the broadest indication of 'prevention of cardiovascular disease' in patients who are currently recommended for all components of a polypill, there remains uncertainty about whether or not large-scale clinical trials on adherence and biomarkers of adherence (e.g. blood pressure, cholesterol) will be sufficient.

Conclusion

In the last decade, significant progress has been made in testing the concept of a cardiovascular polypill. Polypills can reduce cardiovascular risk factors to the same degree as their individual components, without increasing adverse events. Long-term trials with morbidity and mortality outcomes examining the broad use of cardiovascular polypills for primary prevention are ongoing and are several years away from reporting.

Results from trials demonstrating the positive impact of a polypill-based strategy on improving the appropriate use of preventive drugs in people with established indications are already accumulating. Definitive answers are expected to be available in the next 12 months. <

The George Institute for Global Health recently secured an exclusive global license for the polypills used in the SPACE Collaboration trials, following a decision by Dr Reddy's Laboratories Ltd not to proceed with taking the products to market because of existing regulatory requirements.

The George Institute for Global Health has received funding from Dr Reddy's Laboratories to support the secretariat of the SPACE Collaboration. Ruth Webster is the coordinator of the SPACE Collaboration and Anushka Patel is the deputy chair of the SPACE Collaboration's Steering Committee. Anushka Patel is the principal investigator of the Kanyini Guidelines Adherence with the Polypill trial[9], an investigator in UMPIRE and an investigator in the Programme to Improve Life and Longevity trial.[10]

Anushka Patel and Ruth Webster have received funding from Dr Reddy's Laboratories to attend one SPACE Collaboration Investigators meeting.

Q:

SELF-TEST QUESTIONS

True or false?

1. The polypill for primary prevention of cardiovascular disease contains more than one antihypertensive drug.
2. The polypill is more effective than its individual components given alone.

Answers on page 107

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ARTICLE

Allergen immunotherapy

SUMMARY

Allergen immunotherapy reduces the symptoms of allergic disease by inducing tolerance to specific allergens. It can be given sublingually or by subcutaneous injection.

Immunotherapy is the only form of treatment which modifies abnormal immune reactivity to a specific allergen, rather than simply suppressing symptoms. It may alter the natural history of atopic disease.

Allergen immunotherapy is effective for respiratory allergy (rhinitis and asthma) and venom allergy such as bee stings. Currently immunotherapy has no role in the routine management of food allergy, but research is ongoing.

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Key words
allergic rhinitis, anaphylaxis, asthma, venom

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Introduction

Allergen immunotherapy was first reported in the successful treatment of pollen-induced allergic rhinitis in 1911. It reduces the patient's abnormal immunoreactivity to harmless environmental antigens (allergens). The repeated administration of the allergen induces tolerance. A reduction of allergen-induced symptoms should occur within months. After a 3–5 year maintenance period, this benefit should be long-lasting if not permanent.

For most of its history immunotherapy has been given by subcutaneous injection. As injecting an allergen has the potential to cause anaphylaxis, there is an initial cautious 'updosing' phase followed by a prolonged maintenance phase with regular injections. Recently, sublingual administration of allergen has been found to be effective in allergic respiratory disease.

There is evidence from meta-analyses for the efficacy of subcutaneous and sublingual immunotherapy in the management of allergic rhinitis and asthma.[1-3] Subcutaneous immunotherapy is also effective for venom allergy.[4] The relative efficacy of sublingual and subcutaneous immunotherapy in respiratory allergy remains unclear.

Mechanisms of action

Several mechanisms are proposed to contribute to the effect of allergen immunotherapy. They include the induction of IgG 'blocking' antibodies (which inhibit binding of allergen to IgE), T cell anergy, switching of T-helper 2 (allergic phenotype) cells to T-helper 1, and the induction of regulatory T cells which suppress the immune response. However, even in clinically successful immunotherapy, allergen-specific IgE is still present and allergy tests usually remain positive.

Management of allergic diseases

Management of allergen-induced respiratory symptoms starts with the identification of relevant allergens and avoiding them where possible. Oral or topical antihistamines and intranasal corticosteroids can be effective regardless of the specific allergic cause. Immunotherapy is indicated when the patient's symptoms are moderate to severe, symptoms interfere with function or quality of life, avoidance of the allergen is difficult or impossible, and other treatments are unsatisfactory.

It is important to ensure that the allergens used for immunotherapy are the ones that are causing the patient's symptoms. This is established by a history of symptom patterns matching allergen exposure and confirmed by skin prick tests or serum allergen-specific IgE tests.

Immunotherapy for asthma is problematic because asthma is usually multifactorial. Moderate to severe asthma is also a risk factor for adverse reactions to immunotherapy. However, there is evidence that subcutaneous immunotherapy improves bronchial hyperreactivity and reduces symptoms and medicine use for asthma.[3]

In patients who have had anaphylaxis from an insect sting, immunotherapy is highly effective in reducing the risk of reactions to subsequent stings. In Australia, anaphylaxis most commonly occurs from bee stings, but can also be caused by stings from native and imported wasps and Jack-Jumper ants.

Allergens for immunotherapy

Allergens are manufactured for both diagnosis and immunotherapy. They are purified protein extracts from allergenic substances. Diagnostic extracts should be from a single species only and contain all relevant

allergenic proteins. However, allergen extracts are poorly defined pharmacologically and biochemically and poorly standardised. Extracts from different manufacturers vary considerably and this could influence the effectiveness of diagnosis and treatment. Recombinant allergenic proteins are starting to be used in diagnosis, but not yet for therapy.

Common allergen classes in respiratory disease are pollens (grass, weed and tree), dust mites, moulds and animal danders. Pollens tend to cause seasonal rhinitis although seasonal patterns vary with pollen type and region. Other allergens may cause perennial rhinitis, depending on exposure patterns. Allergens from each of these groups are available for immunotherapy.

The allergens used for immunotherapy may be single extracts from an individual species or mixtures of different allergen species. Mixtures of different allergen classes may not be compatible.[5] The patient's sensitisation pattern and major exposures guide the selection of allergens. Many patients are sensitised to multiple allergens either within one of the main classes (for example pollens) or from several classes. This may be due to cross-reactive allergy or due to separate independent sensitisations. It is unclear whether all relevant allergens need to be included in the mixture for optimal results (some mixtures contain potentially suboptimal amounts of each allergen) or whether a small number of key or dominant allergens will suffice.

Paper wasp

European Wasp

Honeybee

Jack-Jumper ant

Treatment

Allergen immunotherapy is usually prescribed by physicians or paediatricians who have received subspecialty training in clinical immunology and allergy. This is to ensure optimal patient and allergen selection and to manage the risks of immunotherapy. Usually therapy begins with weekly injections in an outpatient or clinic setting. Venom immunotherapy may be introduced with a rapid-updosing 'rush' protocol over 2–5 days. This is done in a hospital day-patient setting because of the increased risk of reactions. Most injections can be given by specialists or GPs. Free e-training in immunotherapy is available from the Australasian Society of Clinical Immunology and Allergy.[6] Practitioners need the skill and equipment to be able to manage anaphylaxis (see *Australian Prescriber* wallchart[7]).

Subcutaneous immunotherapy

There are two main ranges of injectable immunotherapy products in Australia:

- an aluminium hydroxide conjugated formula which may be ordered in standard preparations or in individual mixtures
- an aqueous formulation usually prepared by the allergy specialist.

Some allergens are registered therapeutic goods whereas conjugated allergen mixes are available on a named-patient basis. Only certain venom allergens are available on the Pharmaceutical Benefits Scheme. These are for bee, European (*Vespula*) and paper wasp (*Polistes*). Jack-Jumper ant venom immunotherapy is available in some centres (Royal Adelaide Hospital and Royal Hobart Hospital) at the patient's expense.

Subcutaneous immunotherapy is usually effective for symptom reduction. The responses may be partial rather than total, so it should not be assumed that other treatments and avoidance strategies will no longer be needed. In addition, there is a subgroup of patients who do not improve with immunotherapy. This may be because a suboptimal allergen was used or the symptoms were actually caused by non-allergic disease (for example, chronic rhinosinusitis). Sometimes immunotherapy fails for unknown reasons.

Injection technique

Injections of allergen are administered subcutaneously, usually in the posterior part of the upper arm, using a fine gauge needle (26/27G) and 1 mL syringe (insulin syringes are ideal). A complete detailed guide to the administration of subcutaneous immunotherapy injections is available at www.allergy.org.au/health-professionals/papers/scit-treatment-plan.

Adverse effects

Subcutaneous immunotherapy carries risks which include immediate reactions such as anaphylaxis, and delayed reactions such as local swelling and more rarely, exacerbations of asthma or atopic eczema. The risk of immediate reactions can be reduced by premedication with antihistamines, but medical observation for 30–45 minutes after each injection is mandatory, including during the maintenance phase of treatment even if the injections have previously been well tolerated.

Sublingual immunotherapy

Alternative routes of delivery for immunotherapy have been sought to improve safety and ease of use while retaining effectiveness. Sublingual immunotherapy emerged in the mainstream literature in the 1990s. There is now evidence[2] for the efficacy of sublingually administered allergens in respiratory allergy. Higher doses of allergen are required compared with subcutaneous immunotherapy. The allergen is absorbed through the oral mucosa and studies have shown systemic immunological changes similar to those of subcutaneous immunotherapy. The majority of evidence relates to single allergens or oligoallergen mixtures, mainly pollen and mite, in allergic rhinitis, but evidence also exists for efficacy in asthma.

Sublingual immunotherapy is available in tablets or in drop form (pump bottles or plastic ampoules). Liquid drops for sublingual immunotherapy are available to order on a named-patient basis as single allergens or allergen mixtures. The only sublingual immunotherapy tablet currently registered is a fixed composition mixture of five pollens from the rye grass family.

Sublingual immunotherapy is convenient and can be administered at home. Various protocols are currently suggested, although the default is daily treatment for three years (the same total term as subcutaneous immunotherapy). Alternate daily schedules and pre/co-seasonal-only schedules are also used. While the acceptability of sublingual immunotherapy is high, adherence to the full long-term program is poor.[8]

Adverse effects

Sublingual immunotherapy has a substantial safety advantage over subcutaneous injections. It has mostly transient local adverse effects with very few reports of systemic reactions.[9]

Future developments

An important finding in both subcutaneous and sublingual immunotherapy is the potential for altering the natural history of atopy. There is evidence for a reduction in the new onset of asthma[10] in those treated for allergic rhinitis and also a reduction in the incidence of new allergic sensitisations.[11] These findings are intriguing and promising, but require further replication. If confirmed, they suggest that immunotherapy may reduce the overall burden of allergic disease and should be used earlier in allergic respiratory disease, not just when other treatments have failed.

Recombinant allergens or modified (peptide) allergens may provide advantages and are currently in development. Peptides and modified proteins may be constructed in such a way as to avoid IgE-binding. This reduces the risk of anaphylaxis while retaining the T cell epitopes which induce regulatory T cells to suppress allergy.

Immunotherapy for food allergy is not routinely practised and hitherto was considered too risky. However, there has been a great deal of recent investigation into inducing specific oral tolerance for egg, milk and nut allergy. This involves gradual introduction of the allergenic food under carefully controlled conditions. It is still considered a research-only procedure. Concerns remain regarding the considerable risk of acute allergic reactions, the induction of eosinophilic enteritis, and whether permanent tolerance (as opposed to temporary desensitisation) can be achieved. ◅

Conclusion

Allergen immunotherapy is an important modality in the management of respiratory allergic disease and venom allergy. Immunotherapy for respiratory allergic disease has been expanded from the traditional injection method to include sublingual administration which has near-equivalent efficacy. ◅

William Smith has attended an interstate presentation sponsored by Stallergenes, and while at a conference in London, attended a sponsored visit to the Stallergenes factory in Paris. Stallergenes are manufacturers of allergen immunotherapy products.

Q:

SELF-TEST QUESTIONS

True or false?

3. Anaphylaxis can occur during the maintenance phase of injection immunotherapy.

4. Severe asthma increases the risk of an adverse reaction to immunotherapy.

Answers on page 107

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ARTICLE

Nutrients and herbal supplements for mental health

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Key words
anxiety, depression

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SUMMARY

Some nutrient supplements and herbal medicines have supportive evidence for efficacy in some mental health disorders, other products do not.

Omega-3 fatty acids (eicosapentaenoic acid), St John's wort (high quality, standardised extracts), S-adenosyl-methionine and zinc may be beneficial in improving mood.

N-acetyl cysteine has shown some effects in bipolar depression and may be of benefit in obsessive compulsive disorder.

Kava is effective for reducing anxiety. However, there have been concerns about hepatotoxicity.

It is important to be aware of potential drug interactions between prescription drugs, herbal medicines and supplements. Patients should be asked which products they are taking.

Introduction

Mental health concerns are a major reason why people (especially middle-aged women) use nutrient or herbal-based supplements.[1] Due to increased community use, it is important to know which products have evidence of efficacy.

Another consideration for people using supplements is cost. While some products such as folic acid or omega-3 fish oils may be as little as $5 per week, others such as S-adenosyl-methionine may cost up to $70 per week. Quality is also an issue, with variations occurring between products, particularly herbal medicines.[2]

Diet, supplementation and mental health

There are a variety of relationships between diet, supplementation and mental health.

Poor diet as a risk for mental health symptoms

Some nutritional deficiencies, such as vitamin B and zinc, are associated with depression. A diet consisting of processed and 'junk' foods, as opposed to a wholefood diet of lean meats, fish, whole grains, fruit and vegetables, may be a risk factor for mental disorders. After confounding factors such as socioeconomic status were adjusted for, cross-sectional and longitudinal data revealed that poor diet is associated with increased depressive and anxiety symptoms.[3,4]

Dietary supplementation to prevent mental health symptoms

Adding nutrient supplements to the diet has not been shown to prevent the development of psychiatric disorders.

Supplementation to treat mental health symptoms

Several supplements have evidence of therapeutic activity. However, there are some for which there is no consistent supportive evidence. Examples of these include valerian for insomnia, St John's wort in anxiety disorders or attention deficit hyperactivity disorder, N-acetyl cysteine or docosahexaenoic acid (DHA) fatty acids for unipolar depression, and omega-3 for mania. Interestingly, 'adjunctive' prescription of a range of nutrients – such as omega-3 fatty acids, folic acid, N-acetyl cysteine, S-adenosyl-methionine and zinc – with various medicines has been shown to have a beneficial effect in improving treatment beyond that of placebo.[5-7]

Supplements for mood

A number of supplements have been studied for improving general mood or treating major depression. Of these, omega-3 fatty acids, St John's wort, S-adenosyl-methionine, N-acetyl cysteine and zinc are the most researched and commonly used.

Omega-3 fatty acids

Epidemiological studies have shown that a lower dietary intake of omega-3 oils – eicosapentaenoic acid (EPA) and DHA – may be correlated with an increased risk of depressive symptoms.[8] Dozens of clinical trials on major depression have assessed the efficacy of these fatty acids alone or in combination with selective serotonin reuptake inhibitors.[9,10] Clinical trials have not commonly compared omega-3 fatty acids directly with selective serotonin reuptake inhibitors.

A meta-analysis revealed that EPA (or higher ratio of EPA to DHA) supplementation may have a stronger

antidepressant effect than DHA.[11] The comparison found supplements containing more than 50% EPA were significantly better than placebo (p=0.005), whereas there was no significant difference with DHA monotherapy.

In bipolar depression, a meta-analysis of five pooled datasets from 291 patients found a significant effect in favour of omega-3 fatty acids (p=0.029) for reducing depression, with a moderate effect size.[12] The current weight of evidence supports EPA or EPA-rich omega-3 fatty acids as adjunctive treatment in bipolar depression.

S-adenosyl-methionine

Double-blind studies have shown that parenteral and oral preparations of S-adenosyl-methionine are as effective for treating depression as standard tricyclic antidepressants such as clomipramine, amitriptyline and imipramine, and tend to produce relatively fewer adverse effects.[13] In a six-week randomised controlled trial involving 73 patients with major depression, S-adenosyl-methionine added to selective serotonin reuptake inhibitors (SSRIs) produced significantly greater clinical responses and remission rates compared to adding placebo.[14] Aside from being expensive, S-adenosyl-methionine appears well tolerated with only mild adverse effects such as headaches, restlessness, insomnia and gastrointestinal upsets.[15]

St John's wort

St John's wort has been studied for treating depression in over 40 clinical trials of varying methodological quality. A Cochrane review of 29 trials (5489 patients) analysed 18 comparisons of St John's wort with placebo and 17 comparisons with antidepressants. It revealed that participants were significantly more likely to respond to St John's wort than to placebo (relative risk of 1.48, confidence interval 1.23–1.77), but results from the studies were very heterogeneous. In the same analysis, St John's wort had an equivalent effect to SSRIs (relative risk of response 1.00, CI 0.90–1.15).[16]

A long-term follow-up study of St John's wort (standardised European extract WS 5570) for mild to moderate depression assessed remission rates in 426 responders who either continued St John's wort or changed to placebo for 26 weeks.[17] People continuing St John's wort had a significantly longer time in remission. Response to St John's wort was similar to that of SSRIs, with data indicating that an initial partial response is predictive of full response (which usually occurs within 2–4 weeks).[18]

Because of the risk of drug interactions (see Drug interactions with complementary medicines, Aust Prescr 2010;33:177-80), people taking other medicines should only use St John's wort with low hyperforin (<4 mg per tablet). Products standardised for higher amounts of hypericin and flavonoids should not induce cytochrome enzymes.[19] Amounts of hypericin are usually identified on St John's wort products, however hyperforin quantities are often not detailed. St John's wort should not be taken with antidepressants as serotonin syndrome can occur.

N-acetyl cysteine

N-acetyl cysteine is an amino acid with strong antioxidant properties and has a history of use in the management of paracetamol overdose. It has been found to significantly reduce depression in bipolar disorder. In a 24-week placebo-controlled trial of 75 people with bipolar disorder, 1 g of N-acetyl cysteine twice per day significantly reduced depression on the Montgomery-Asberg Depression Rating Scale (p=0.002).[20] N-acetyl cysteine appears to cause no common significant adverse effects. Currently, it is only available from compounding pharmacies or from overseas.

Zinc

There is emerging evidence that zinc improves depressed mood. A recent review of randomised controlled trials found four studies (pooled sample of 469 participants) that met inclusion criteria.[6] In two of the studies that used zinc monotherapy (sample sizes of 60 and 20), zinc as an adjunct to antidepressants significantly lowered depression (p<0.001) at 12 weeks. Zinc can be safely prescribed up to 30 mg elemental per day, with amino acid or picolinate chelations being advised to improve absorption. Zinc may cause nausea on an empty stomach.

Multivitamins

Multivitamins (in particular formulations high in B vitamins) may provide an acute mood enhancement and decreased perceived stress. A meta-analysis of eight studies involving a pooled sample of 1292 people revealed that supplementation for a duration of at least 28 days reduced perceived stress (p=0.001), mild psychiatric symptoms such as low mood (p=0.001) and anxiety (p<0.001), but not depression (p=0.089).[21] A recent 16-week randomised controlled trial of 182 participants found that while qualitative data revealed an improvement in mood and energy with multivitamins,[22] the quantitative data did not support any effect beyond placebo.[23] The authors concluded that while an acute effect may occur directly after supplementation, this is diminished after the supplement is withdrawn, with no chronic effect occurring.

Supplements for anxiety

While several herbal medicines have been studied in anxiety, data are largely absent for nutrients. The most researched and used herbal medicine in the treatment of anxiety is kava. Other limited research indicates a possible beneficial effect for ginkgo, passionflower, chamomile, skullcap, lemon balm and bacopa.

Kava

Occasionally, patients may be taking kava. This is a perennial plant native to various regions of the South Pacific.[24] The roots are traditionally prepared as a water-based beverage which has medicinal and psychotropic properties.[25] Water-soluble extracts are available in Australia at maximum daily doses of 250 mg of kavalactones, approximately four to five tablets per day. While kava has been implicated in cases of abuse in the Northern Territory, commonly in combination with alcohol, research has shown it is not addictive when used at therapeutic doses.[26]

A Cochrane review of kava for various anxiety disorders, involving seven studies with a pooled sample size of 380 participants, found a statistically significant mean reduction of 3.9 points on the Hamilton Anxiety Scale over placebo.[27] This result is comparable to antidepressant medicines. Another analysis of kava studies revealed a similar conclusion, with a positive result occurring in four out of six studies.[24] In a recent six-week placebo-controlled trial involving 75 participants with generalised anxiety disorder and no comorbid mood disorder, kava (120 mg titrated to a maximum of 240 mg of kavalactones per day after three weeks if the patient was not responding) reduced anxiety compared to the placebo, with a moderate effect size (p=0.046).[28] No other significant differences between groups occurred for any other adverse effects including liver function. Further research should compare kava to an established treatment for anxiety, such as cognitive behavioural therapy.

Kava was withdrawn from European and UK markets in 2002 due to concerns over reported hepatotoxicity. This may have been due to previous preparations being made using acetone or ethanol extractions from potentially contaminated or poorly stored material, or other parts of the plant.[29,30] Use of only the peeled roots from noble cultivars using a water solute extraction method is advised (see the kava fact sheet by the Therapeutic Goods Administration www.tga.gov.au/safety/alerts-medicine-kava-050421.htm). Occasional liver function tests should be performed during regular use. Alcohol and benzodiazepines should be avoided.[31] Currently no safety data support or refute the use of kava concurrently with antidepressant drugs, and caution is urged.

N-acetyl cysteine

The role of glutamate dysfunction in obsessive compulsive disorder and related disorders, such as compulsive hair pulling[32] or skin picking, has been established. N-acetyl cysteine, a glutamate modulator, has been studied as a treatment for these disorders.

A 12-week double-blind randomised controlled trial involving 48 patients with obsessive compulsive disorder was conducted in Iran.[33] N-acetyl cysteine was titrated from 600 mg/day to a maximum of 2400 mg/day. Symptom severity was assessed at four week intervals. N-acetyl cysteine was significantly better than placebo for ameliorating symptoms according to the Yale-Brown Obsessive Compulsive Disorder scale (p=0.003). N-acetyl cysteine has a good tolerability profile.

Supplements for cognition

Due to our ageing population, increasing research is being conducted on supplements that may have a beneficial role for cognition. Current data do not support this approach to prevent dementia. The greatest area of research concerns multivitamins, and the plant medicines ginkgo and bacopa. Other plants less well studied include lemon balm and sage, in addition to polyphenols from cocoa, pinebark and tea. Although adequate vitamin and nutrient concentrations are necessary for neurological functioning, there is no scientific agreement as to whether they prevent cognitive decline or enhance mental functioning. While a dietary deficit of omega-3 fatty acids may negatively affect cognition, supplementation appears to not exert any significant pro-cognitive effects.

Multivitamins

A meta-analysis of 10 randomised controlled trials (≥1 month) involving 3200 people found that oral multivitamins were effective in improving immediate free recall memory (p<0.01), but not verbal fluency (p=0.26) or delayed free recall memory (p=0.33).[34]

Ginkgo

Ginkgo, in particular the standardised extract 761, has been studied for cognitive-enhancing properties for several decades. Initial research suggested it was superior to placebo in enhancing cognitive function and quality of life and reducing neuropsychiatric symptoms (such as low mood) in patients with mild to moderate dementia, and that it had additive effects with donepezil.[35] However, this appears not to be the

case. A recent randomised controlled trial involving 2854 adults aged 70 years or older, who had reported problems with their memory, found that ginkgo (120 mg extract 761 twice per day) did not reduce the risk of progression to Alzheimer's disease compared to placebo. After five years, 61 participants in the ginkgo group had been diagnosed with probable Alzheimer's disease (1.2 cases per 100 person-years) compared with 73 in the placebo group (1.4 cases per 100 person-years, p=0.306).[36]

Ginkgo has several potential drug interactions.[37] It should not be used concurrently with anticoagulant and antiplatelet medicines, and should not be taken in the week before surgery.

Conclusion

Patients take a range of nutrient and herbal-based supplements for a number of mental health problems. While there is evidence of efficacy for some supplements, for many there are little or no data.[2] Prescribers should be mindful of differences between the quality and standardisation of supplements, and potential drug interactions.[37] ◁

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Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Bexsero meningococcal B vaccine – enhanced monitoring

The TGA has been undertaking enhanced monitoring of the recently launched meningococcal B vaccine, Bexsero.

Bexsero is the first vaccine in Australia intended to prevent invasive meningococcal disease caused by strains of *Neisseria meningitidis* serogroup B (meningococcal B).

Bexsero is indicated for immunisation of patients aged two months and older. For infants aged under six months, three primary doses of Bexsero, plus a booster at 12 months of age, are recommended. Fewer doses are required for older age groups.

According to the National Notifiable Diseases Surveillance System, the majority of invasive meningococcal disease in Australia is caused by group B (84% in 2011–12). The highest incidence of group B disease occurs in children aged under five years, particularly infants aged under 12 months. A lower, secondary peak in incidence has been observed in late adolescence and early adulthood.

As with many other vaccines, patients may experience a rise in temperature following vaccination with Bexsero.

Pre-market evaluation

During pre-market evaluation of Bexsero, the TGA identified that use of the vaccine commonly induced fever in infants and children, including high fever, which is a risk factor for inducing a seizure.

When fever occurred, it generally followed a predictable pattern starting within six hours after vaccination. In the majority of cases, the fever had ceased by the next day.

Information for health professionals

The Australian Technical Advisory Group on Immunisation has recommended the prophylactic use of paracetamol for children aged under two years to reduce the probability and severity of fever.

It is recommended that the first dose of paracetamol (15 mg/kg per dose) be given within the 30-minute period before vaccination or as soon as practicable afterwards. This can be followed by two more doses given six hours apart.

Control of fever alone may not necessarily prevent the development of a seizure.

If you haven't done so already, read the Product Information for Bexsero. Further information is also available in the Australian Technical Advisory Group on Immunisation statement, which is available on the Department of Health's Immunise Australia Program website.

To help the TGA monitor the ongoing safety and risk profile for Bexsero, you are encouraged to report any seizures with a suspected link to the administration of this vaccine, including:

- both febrile and afebrile seizures
- whether Bexsero was administered singly or in combination with other vaccines
- whether an accompanying anti-fever medicine, such as paracetamol, was used or not.

The TGA is regularly reviewing all adverse event reports associated with Bexsero, as well as all other relevant safety information.

For clinical advice about the use of Bexsero, visit the Immunise Australia website.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Strontium ranelate and cardiovascular and venous thromboembolic risks

The Product Information for strontium ranelate has been updated following the completion of a TGA review into the medicine's benefit–risk profile.

Strontium ranelate is used to treat severe osteoporosis in postmenopausal women who are at high risk of fracture and men who are at increased risk of fracture. It is marketed in Australia under the brand name Protos.

The Product Information (PI) changes include an update to the indications requiring that strontium ranelate only be used if all other treatments are deemed unsuitable, either due to contraindications or intolerance. Other changes emphasise the contraindications, reinforce precautions, highlight the need for regular monitoring and update data relating to the risk of adverse events.

A black box warning has also been added to the PI, which summarises the changes.

Black box warning in strontium ranelate Product Information

Protos should only be used when other medications for the treatment for osteoporosis are considered unsuitable. Protos is contraindicated and must not be used in patients with established, current or past history of: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, uncontrolled hypertension, venous thromboembolism, pulmonary embolism. It should also not be used in patients who are temporarily or permanently immobilised. Protos should be used with caution in patients with risk factors for cardiovascular events or venous thrombosis: hypertension, diabetes, smoking, hyperlipidaemia. All patients prescribed Protos should be fully informed of the risk of cardiovascular events and venous thrombosis. Patients should be regularly monitored, every six months.

Safety data

Data from randomised controlled trials show that strontium ranelate is associated with an increased risk of myocardial infarction and venous thromboembolism.

In pooled randomised placebo-controlled studies of postmenopausal osteoporotic patients, a significant increase of myocardial infarction was observed in patients treated with strontium ranelate as compared to placebo (5.7 per 1000 patient-years vs 3.6 per 1000 patient-years), with a relative risk of 1.6 (95% CI 1.07–2.38).

In phase III studies, venous thromboembolism occurred in 2.7% of patients in the strontium ranelate group and 1.9% of those in the placebo group, with a relative risk of 1.4 (95% CI 1.0–2.0).

Information for health professionals

Health professionals are encouraged to read the updated PI and advise patients of the potential cardiovascular and venous thromboembolic adverse events associated with strontium ranelate.

In particular, note that strontium ranelate should only be used if all alternative treatments are considered unsuitable.

Strontium ranelate is contraindicated in patients who have:

- history of ischaemic heart disease, peripheral arterial disease or cerebrovascular disease
- systolic blood pressure greater than or equal to 160 mmHg, or diastolic blood pressure greater than or equal to 90 mmHg
- current or previous venous thromboembolic events, including deep vein thrombosis and pulmonary embolism
- temporary or permanent immobilisation (for example, post-surgical recovery or prolonged bed rest)
- severe renal impairment
- known hypersensitivity to strontium ranelate or to any of the excipients.

Treatment should be stopped if the patient develops any of these conditions after being prescribed this drug.

If the patient becomes immobilised, treatment can be resumed if the event or illness causing the immobilisation is resolved and mobility returns.

Patients should be evaluated for relevant risk factors, including hypertension, diabetes, smoking, hyperlipidaemia, before being treated with strontium ranelate. Patients receiving ongoing treatment with strontium ranelate should be monitored every six months.

You are encouraged to report to the TGA any suspected adverse events associated with strontium ranelate. This will assist the TGA to monitor the safety of this drug.

MEDICINES SAFETY UPDATE

Complex regional pain syndrome and vaccines

A small number of cases of complex regional pain syndrome following vaccination have been reported to the TGA. Health professionals are advised to be mindful of the potential for this adverse event when administering vaccinations and are encouraged to report any suspected cases to the TGA.

Complex regional pain syndrome (CRPS) is characterised by continuing pain that is disproportionate to any potential inciting event, when accompanied by sensory, motor, vasomotor and sweating/oedema signs and symptoms.[1]

There are two forms of CRPS, type 1 (CRPS-I) and type 2 (CRPS-II). CRPS-I is more common and describes a situation in which the patient does not have demonstrable nerve injury. CRPS-II tends to be more serious and describes a situation in which the patient has confirmed nerve injury.

While the cause of CRPS is unknown, it has been diagnosed after trauma, infection, surgery, cervical radiculopathy and myocardial infarction, as well as following vaccination.

The TGA has received five adverse event reports following vaccinations that are consistent with CRPS. Three of those cases involved a human papillomavirus vaccine. Of the other two reports, one involved an influenza vaccine and the other related to diphtheria-tetanus-acellular pertussis vaccination. Some other reports that listed CRPS as an adverse event did not meet the diagnostic criteria.

As part of a recent review of CRPS following vaccination, the TGA referred the issue to its Advisory Committee on the Safety of Vaccines for consideration.

The Committee noted that cases of CRPS were hard to capture, as there was a large variation in causes, but advised that CRPS following vaccination would have been triggered by the pain caused by the process of immunisation, rather than the contents of the vaccine itself.

Three cases of CRPS involving human papillomavirus vaccine in Australia were examined in an article in 2012, which found that:

> intramuscular immunisation is sufficient painful stimulus to trigger the development of CRPS-I, and that it is the process of a needle penetrating the skin that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related.[2]

Given that all vaccines had the ability to cause some degree of trauma, the Advisory Committee on the Safety of Vaccines deemed CRPS following vaccination was under-reported in Australia.

Following consideration of Australian and international data, the TGA review has concluded that CRPS following vaccination with any vaccine is a very rare event. However, there may be under-diagnosis and/or under-reporting of this adverse event in Australia.

The TGA will continue to monitor this issue.

Information for health professionals

Health professionals should be aware of the potential for CRPS following vaccination with any vaccine.

While the TGA concluded that this issue is very rare, you are encouraged to report any suspected cases of CRPS following vaccination. This will assist the TGA in monitoring the safety of vaccines.

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MEDICINES SAFETY UPDATE

Azathioprine and cytomegalovirus reactivation

Information about the risk of cytomegalovirus reactivation in patients with inflammatory bowel disease has been added to the Product Information for azathioprine.

Azathioprine is used as an immunosuppressant antimetabolite. It can be used alone or in combination with corticosteroids and/or other immunosuppressive drugs and procedures.

Cytomegalovirus (CMV) is a common viral infection that normally remains dormant until reactivated when T-lymphocyte mediated immunity is compromised. CMV viraemia can lead to secondary haemophagocytic syndrome.

The Product Information (PI) update is the result of a TGA review of two cases of CMV reactivation associated with oral use of azathioprine.[1] The precautions section of the PI now advises that CMV viraemia resulting in severe pneumonitis and haemophagocytic syndrome in patients with inflammatory bowel disease has been reported in the literature. It recommends that caution be exercised and specialist literature consulted when assessing the risk of CMV reactivation and inflammatory bowel disease deterioration.

Four cases of CMV reactivation and/or haemophagocytic syndrome associated with azathioprine have been reported to the TGA since 1992.

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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:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

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

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Medicines Safety Update is written by staff from the Office of Product Review

DIAGNOSTIC TESTS

Glycated haemoglobin for the diagnosis of diabetes

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Key words
blood glucose, diabetic retinopathy, HbA1c, hyperglycaemia

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SUMMARY

The development of specific diabetes complications correlates with glycated haemoglobin (HbA1c), the most accepted measure of chronic glycaemia.

An HbA1c of 48 mmol/mol (6.5%) or greater has now been recommended in Australia for diagnosis of type 2 diabetes.

The HbA1c test should greatly simplify the diagnostic pathway, negating the need for oral glucose tolerance tests in the majority of patients. However, improved performance and precision of the assay with its standardisation across Australia is required.

Many clinical situations can impact on the HbA1c assay and the clinician needs to be aware of these if it is to be used appropriately for diagnosis.

Introduction

Diabetes results from elevated blood glucose and its diagnosis has traditionally been estabished by measuring blood glucose. The current blood glucose criteria used for diagnosis are associated with an increased risk of diabetes-related complications.

The major disease burden of type 2 diabetes is from macrovascular disease. There is a strong relationship between elevated blood glucose and coronary heart disease. Unfortunately, there is no threshold of blood glucose concentration associated with the development of coronary heart disease so the diagnosis cannot be related to macrovascular risk.[1]

In contrast, there is a clear glycaemic threshold for the development of microvascular complications, particularly diabetic retinopathy. There are also excellent outcome data showing that glucose-lowering therapy effectively prevents these complications.[2] The modern diagnosis of diabetes has therefore been based on blood glucose criteria associated with the development of retinopathy.[3,4] Over time, these blood glucose criteria have changed as the understanding of their relationship to retinopathy has improved.[5]

Blood glucose testing

The reliability of a blood glucose test performed in a laboratory is taken for granted by most medical practitioners. However, there are major practical problems with the fasting blood glucose and the oral glucose tolerance tests.

The day to day variation of blood glucose is considerable. The concentration of blood glucose ex vivo falls quickly even when collected in a fluoride tube, and the inter-laboratory results vary by at least 14% in a third of cases.[6,7]

With the oral glucose tolerance test, the patient should be on an appropriate diet for three days beforehand and have had a satisfactory period of overnight fasting. The test is time consuming to perform, taking at least two hours and involving three blood glucose samples. It is also labour intensive for pathology laboratories. The test is poorly tolerated by a significant number of people, with nausea, vomiting, delayed gastric emptying and issues of venous access all contributing to an invalid test. It often needs to be repeated and has poor patient compliance. A recent study from the Flinders Medical Centre in South Australia showed that only 27% of patients identified on admission as potentially having diabetes presented for a diagnostic oral glucose tolerance test despite repeated contact.[8]

Glycated haemoglobin (HbA1c) testing

Glycated haemoglobin (HbA1c) is produced by the non-enzymatic glycation of haemoglobin. The degree of glycation reflects the mean plasma glucose over the life of the red blood cell (approximately three months). Testing HbA1c is attractive as it measures chronic glycaemia rather than instantaneous blood glucose. It has been used as an objective marker of average glycaemic control for many years and has an accepted place in the monitoring of patients with diabetes. A review of eight studies conducted between 1988 and 2004 reported that HbA1c concentrations above 48 mmol/mol (6.5%) were at

least as strongly correlated with the development of diabetic retinopathy as blood glucose concentrations.[9] HbA1c is also associated with macrovascular outcomes and mortality, although there is no threshold below which there is no risk.[1,10,11]

HbA1c testing provides significant practical advantages over blood glucose measurement. It can be performed at any time of the day and does not require any special pre-test preparation by the patient. The blood sample is stable once collected – essentially in the same tube used for a full blood count. When access to an appropriate laboratory is limited, the test can be performed using a point-of-care testing machine. This may be particularly useful in rural and remote areas.

Standardisation

HbA1c testing must be reliable and consistent across Australia. The US National Glycohemoglobin Standardization Program has driven improvements in assays.[12] The variability of different tests for HbA1c within Australia is now acceptable. In a recent Australian study, whole blood samples were sent to more than 200 laboratories for testing. More than 90% of HbA1c results fell within 6% of the median.[13] Further improvements in standardisation should be achieved following the development of a national quality control program by the Royal College of Pathologists of Australasia, the Australian Association of Clinical Biochemists and the Australian Diabetes Society. Standardisation and calibration are extremely important if point-of-care testing is used for establishing the diagnosis.

Limitations

There are a number of clinical conditions which may affect the accuracy of the test, resulting in falsely high or low readings. The major concern is of a falsely low HbA1c result being interpreted as being normal in a patient with true diabetes. This may delay diagnosis, with the potential for significant long-term consequences. It is very important that clinicians are fully aware of the test's limitations. Any condition that leads to a shortened red cell survival time can interfere with the HbA1c assay. This includes the haemoglobinopathies, therapeutic venesection, anaemia, haemolysis, recent transfusion, and chronic renal failure. If any of these conditions are thought to exist, the diagnosis should be made on measures of blood glucose.[6,7,14] The effect of haemoglobinopathies is complex, varying with the type of haemoglobinopathy, the instrument and the method used in the laboratory. If suspected, discuss this issue with your local chemical pathology laboratory. If a patient has had a therapeutic venesection or a transfusion, the test should be delayed for three months, until the HbA1c measurement will be valid.

Recommendations

Along with other international organisations,[15,16] the Australian Diabetes Society has recommended that an HbA1c of 48 mmol/mol (6.5%) can be used to establish the diagnosis.[13] This recommendation is to be used in conjunction with National Health and Medical Research Council guidelines for the management of type 2 diabetes.[17] In the absence of symptoms, a second elevated HbA1c is necessary to confirm the diagnosis.

Currently in Australia, an HbA1c test can only be reimbursed by Medicare in patients with established diabetes. The Australian Diabetes Society has submitted a proposal to Medicare to accept the measurement of HbA1c for diagnosis but this proposal is still under consideration.

Discrepancies between blood glucose and HbA1c tests

HbA1c is a measure of chronic glycaemia whereas blood glucose tests are acute measurements at one point in time. These tests will identify different populations of patients. Most people with elevated blood glucose will have a raised HbA1c. However, some patients with a minor elevation on the fasting blood glucose or oral glucose tolerance tests will have an HbA1c of less than 48 mmol/mol (6.5%) (the diagnostic threshold). How does a practitioner resolve this discrepancy? Usually, the blood glucose concentrations are only minimally raised in these patients and the HbA1c result implies that they are at minimal or no risk of developing microvascular complications.[9-11] Although their blood glucose results are consistent with the biochemical diagnosis, they do not have chronic hyperglycaemia which is associated with an increased risk of developing microvascular complications. This means they do not have clinically relevant diabetes. These patients should still be assessed for their risk of macrovascular diseases, and their blood pressure and lipids managed appropriately. The test should be repeated.

Pregnancy

HbA1c cannot be used to diagnose diabetes in pregnancy. If true diabetes in pregnancy is suspected, blood glucose criteria must be used.

Conclusion

The acceptance of HbA1c testing will provide an additional tool to assist in the early diagnosis of diabetes. But it should not be the only tool. There remains a very important role for blood glucose testing, and the medical practitioner needs to be aware of the

benefits and limitations of both strategies. However, the HbA1c test does overcome many of the practical problems associated with the fasting blood glucose or oral glucose tolerance tests and its correct use should enhance the early diagnosis of type 2 diabetes. ◀

Conflict of interest: none declared

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New drugs

Crizotinib

Approved indication: non-small cell lung cancer
Xalkori (Pfizer)
200 mg and 250 mg capsules
Australian Medicines Handbook section 14.2.3

Along with erlotinib (Aust Prescr 2006;29:53-5) and gefitinib (Aust Prescr 2003;26:94-5), crizotinib is an oral tyrosine kinase inhibitor for non-small cell lung cancer – it is indicated for people with anaplastic lymphoma kinase (ALK)-positive advanced disease. Rearrangements in this gene lead to continuous activation of the kinase which promotes cell proliferation and inhibits apoptosis. Up to 5% of people with non-small cell lung cancer will have mutated ALK. These are mainly adenocarcinomas and are more likely to occur in non-smokers.

Following an oral dose, peak concentrations are reached after 4–6 hours. Steady state is reached after 15 days with twice-daily dosing. After extensive metabolism in the liver, most of the dose is eliminated in the faeces (63%) and urine (22%). The terminal half-life is 42 hours. Drug concentrations are likely to increase in hepatic impairment so caution is urged in these patients. Dose reduction is needed in people

with severe renal impairment (creatinine clearance <30 mL/min).

After showing antitumour activity in two single-arm trials[1,2], a phase III trial compared oral crizotinib to intravenous chemotherapy. Patients with locally advanced or metastatic ALK-positive disease despite platinum-based chemotherapy were enrolled. More people responded to crizotinib than to chemotherapy and progression-free survival was significantly longer (see Table). This trend was not reflected in overall survival time which was slightly shorter in people receiving crizotinib. However, people in the chemotherapy group were allowed to cross over to the crizotinib group once their disease progressed.[3]

The most common adverse events with crizotinib were vision disturbances (60% of patients), diarrhoea (60%), nausea (55%), vomiting (47%), constipation (42%), oedema (31%), fatigue (27%), upper respiratory tract infection (26%), dysgeusia (26%), dizziness (22%), neuropathy (19%), dyspnoea (13%), rash (9%) and alopecia (8%).[3] Some patients with vision problems had to have their dose reduced or interrupted.

Hepatotoxicity and interstitial lung disease have occurred with this drug, often in the first two months of treatment. In the phase III trial, 16% of patients had severe elevations in liver enzymes (grade 3 or 4). Two patients had to stop treatment and one patient died of hepatic failure.[3] Liver function should be monitored every month and dose reduction is recommended if elevations occur. Two patients taking crizotinib died from interstitial lung disease/pneumonitis.[3] Treatment should be discontinued permanently if symptoms develop.

QTc prolongation has been observed with crizotinib and ECG monitoring should be considered in patients who have or may develop a prolonged QT interval. Symptomatic bradycardia can also develop after several weeks of treatment so pulse and blood pressure should be measured each month. Avoid using crizotinib with drugs that slow the heart rate, including beta blockers, verapamil, diltiazem or digoxin. Crizotinib may need to be permanently stopped if severe QTc prolongation or severe bradycardia occur.

Severe neutropenia (13% of patients) and leucopenia (5% of patients) occurred with crizotinib.[3] White blood cell counts should be measured and dose reduction or interruption is recommended if these abnormalities occur.

Crizotinib is a substrate and a moderate inhibitor of cytochrome (CYP) P450 3A4/5 so has numerous potential drug interactions. Concomitant use of strong CYP3A inhibitors (some protease inhibitors and azole antifungals, grapefruit juice) or inducers (carbamazepine, rifampicin and St John's wort) may affect plasma concentrations of crizotinib and should be avoided.

Co-administration of drugs with a narrow therapeutic index that are mainly metabolised by CYP3A4 (including cyclosporin, fentanyl and sirolimus) is not recommended. Also avoid CYP3A substrates with a narrow therapeutic index and the potential to cause fatal arrhythmias (dihydroergotamine, ergotamine).

Crizotinib seems to significantly prolong progression-free survival in patients with non-small cell lung cancer, but its effect on overall survival is unclear. Confirmation that a patient has ALK-positive disease is needed before treatment can start. Prescribers and patients should be aware of the life-threatening adverse events that can occur with this treatment.

T manufacturer provided the AusPAR and the product information

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Table **Efficacy of crizotinib in a comparative phase III trial** [3]

	Crizotinib (250 mg twice daily)	Chemotherapy (pemetrexed 500 mg/m² body surface or docetaxel 75 mg/m² body surface every 3 weeks)
Number of patients	173	174
Progression-free survival	7.7 months	3 months
Treatment response	1 complete response 112 partial responses	0 complete responses 34 partial responses
Median overall survival	20.3 months	22.8 months

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Pasireotide diaspartate

Approved indication: Cushing's disease
Signifor (Novartis)
ampoules containing 900 microgram/mL
Australian Medicines Handbook section 10.6.6

Cushing's disease is caused by pituitary adenomas which secrete adrenocorticotrophic hormone (ACTH). Surgical treatment helps most patients, but some do not enter remission and others relapse. Pasireotide is an option for these patients and is also indicated for those who cannot have surgery.

The pituitary adenomas contain receptors for somatostatin (growth hormone release inhibiting factor). Pasireotide is an analogue of somatostatin which binds to these receptors. This inhibits the secretion of ACTH.

To test the hypothesis that pasireotide would work in Cushing's disease the drug was injected twice a day by patients who had 24-hour urinary free cortisol at least twice the upper limit of normal. After 15 days, 22 of 29 patients had reduced cortisol. In five of them, the urinary cortisol returned to normal. Average concentrations of plasma ACTH and serum cortisol also reduced.[1]

A phase III trial studied 162 patients with Cushing's disease who had levels of 24-hour urinary free cortisol at least 1.5 times the upper limit of normal. They were randomised to receive twice-daily injections of pasireotide 600 microgram or 900 microgram. If the urinary cortisol level was more than twice the upper limit of normal after three months, the dose was increased by 300 microgram twice daily for a further three months. The primary end point of the double-blind trial was at six months, but the trial continued with an open-label phase for a further six months. The mean duration of treatment was 10.8 months.[2,3]

Urinary free cortisol declined rapidly. By six months 15% of the patients given 600 microgram and 26% of those given 900 microgram had levels within the normal range. After 12 months the corresponding figures were 13% and 25%. Clinical changes at 12 months included an average weight loss of 6.7 kg and decreased mean blood pressure (–6.1 mmHg systolic, –3.7 mmHg diastolic). There were also improvements in triglycerides and low density lipoprotein cholesterol.[2]

Glucose intolerance is common in Cushing's disease, but this did not improve with treatment. By the end of the study 51 of the 107 patients who did not have diabetes at the start of the study had become diabetic (glycated haemoglobin of more than 48 mmol/mol or 6.5%). A new hypoglycaemic drug had to be started in 74 of the 162 patients in the phase III trial.[2]

Pasireotide is given by subcutaneous injection preferably into the abdomen or top of the thigh. Approximately 17% of patients will have injection-site reactions. Although pasireotide is not metabolised it is eliminated in the bile so liver disease will increase exposure to the drug. Approximately 30% of patients develop cholelithiasis,[2] so ultrasound scans of the gall bladder are recommended before and during treatment. Liver enzymes can increase so liver function tests are recommended before treatment, after one or two weeks and then monthly for the first three months of treatment. Sustained changes in liver function are an indication for stopping pasireotide permanently. Severe liver disease is a contraindication.

The most frequent adverse effects of pasireotide are nausea and diarrhoea. Abdominal pain and headache are also common. In some patients the reduction in cortisol in response to pasireotide caused symptoms of hypocortisolism. Hypopituitarism can also occur. The drug can prolong the QT interval on the ECG and cause bradycardia. There is therefore a risk of interaction with drugs such as beta blockers and antiarrhythmic drugs. There have been no clinical studies of drug interactions. There were also no studies in children, pregnant or lactating women.

Only a minority of patients have a complete response to pasireotide. In the phase III trial only 48% of the patients continued the drug for 12 months.[2] The main cause of discontinuation was lack of efficacy. Increasing the dose may not increase efficacy. The drug should probably be stopped if there has been no response after two months of treatment. The combination and comparison of pasireotide with other treatments requires further research.

T T manufacturer provided additional useful information

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Regorafenib

Approved indication: colorectal cancer
Stirvarga (Bayer)
40 mg tablets
Australian Medicines Handbook section 14.2.3

Regorafenib is indicated for patients with metastatic colorectal cancer who have had previous treatment with multiple regimens (chemotherapy, targeted anticancer therapies). Life expectancy is generally only a few months for these patients.

Regorafenib is a protein kinase inhibitor with a similar structure to sorafenib (Aust Prescr 2006;29:167-71). It is thought to work by inhibiting multiple signalling pathways involved in angiogenesis and tumour growth.

The approval of regorafenib is based on a phase III placebo-controlled trial of 760 adults with progressive colorectal cancer despite treatment. Only patients with a life expectancy of at least three months were enrolled and those with CNS metastases were excluded. Oral regorafenib 160 mg or placebo was given once a day for three weeks of a four-week cycle until disease progressed or patients had unacceptable adverse effects. Although overall survival was approximately six weeks longer with regorafenib than with placebo, progression-free survival was similar between groups. Stable disease was more common with active treatment than with the placebo (41% vs 15%) (see Table).[1]

Adverse effects were very common with regorafenib and many patients had to have their dose modified or interrupted. Over half of the participants had a serious (grade 3 or 4) regorafenib-related event. The most frequently reported serious reactions were hand–foot skin reactions (17%), fatigue (9%), diarrhoea (7%), hypertension (7%), rash (6%) and oral mucositis (3%). Myocardial ischaemia and reversible posterior leukoencephalopathy have also occurred in patients taking regorafenib.

Eight of the 505 patients in the regorafenib group died because of an adverse event. Causes included pneumonia (2 cases), gastrointestinal bleeding (2 cases), intestinal obstruction (1 case), pulmonary haemorrhage (1 case), seizure (1 case) and sudden death (1 case).[1]

Fatal drug-induced liver failure has been reported with regorafenib. Liver function tests are therefore recommended before and during treatment and dose reductions may be needed if liver function declines. There is an increased risk of bleeding so blood counts and coagulation should be monitored, especially in patients receiving concomitant anticoagulants.

Electrolyte abnormalities can occur with this drug and monitoring is recommended during treatment. As with other anti-angiogenic drugs, wound healing may be delayed and regorafenib treatment should be stopped two weeks before surgery.

Regorafenib tablets should be taken with a low fat meal. Following a 160 mg dose, peak plasma concentrations are reached after 3–4 hours. Regorafenib is metabolised in the liver and its elimination half-life is 20–30 hours. The drug and its metabolites are excreted in the faeces (71%) and urine (19%). Close monitoring is recommended with severe renal or hepatic impairment as there is limited drug experience in these patients.

Regorafenib is mainly metabolised via cytochrome (CYP) 3A4 and uridine diphosphate glucuronosyl transferase UGT1A9. Concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole and grapefruit juice) and inducers (e.g. phenytoin, dexamethasone and St John's wort) should be avoided. Regorafenib also inhibits P-glycoprotein so may increase concentrations of concomitant drugs affected by this transporter such as digoxin. Co-administration of regorafenib with antibiotics that affect the gut flora may reduce regorafenib's efficacy.

Table **Efficacy of regorafenib in metastatic colorectal cancer**[1]

	Treatment	
	Regorafenib + best supportive care	**Placebo + best supportive care**
Number of patients	505	255
Mean duration of treatment	2.8 months	1.8 months
Median overall survival	6.4 months	5 months
Median progression-free survival	1.9 months	1.7 months
Response to treatment	No complete responses 5 partial responses 207 patients (41%) had stable disease	No complete responses 1 partial response 38 patients (15%) had stable disease

For patients with metastatic disease who have no other therapeutic options, regorafenib improves survival time by approximately six weeks. Its main effect seems to be to keep the disease stable. However, regorafenib causes considerable adverse affects which are often severe and sometimes fatal.

T manufacturer provided the AusPAR

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Tenofovir disoproxil fumarate, emtricitabine, elvitegravir, cobicistat

Approved indication: HIV

Stribild (Gilead)

film-coated tablets containing tenofovir 300 mg, emtricitabine 200 mg, elvitegravir 150 mg, cobicistat 150 mg

Australian Medicines Handbook section 5.4

Preferred combinations for initial antiretroviral therapy include two nucleos(t)ide reverse transcriptase inhibitors (e.g. tenofovir and emtricitabine) plus a non-nucleoside reverse transcriptase inhibitor (e.g. efavirenz) or a protease inhibitor (e.g. atazanavir) (http://arv.ashm.org.au).

This product is a fixed-dose combination of tenofovir (Aust Prescr 2002;25:147-51) and emtricitabine (Aust Prescr 2005;28:49-51), which are already available in other combination products. It also contains two newly approved drugs – elvitegravir, an HIV-1 integrase inhibitor, and cobicistat, a pharmacokinetic enhancer.

Elvitegravir, similar to raltegravir (Aust Prescr 2008;31:49-55), works by preventing the insertion of viral DNA into host genomic DNA. However, on its own, elvitegravir's bioavailability and half-life is limited by cytochrome P450 (CYP) 3A-dependent metabolism. Cobicistat increases the exposure of elvitegravir by inhibiting CYP3A4, but has no direct antiretroviral properties.

The efficacy of this combination drug has been assessed in two actively controlled non-inferiority trials totalling 1408 previously untreated patients with HIV (see Table).[1,2] Only 8–12% of these people were women, which is representative of the Australian HIV population.‡ At enrolment, participants had to have at least 5000 HIV RNA copies per mL of blood and be susceptible to the antivirals used in the trials. Those with AIDS-defining disorders or serious infections were excluded.

The combination of tenofovir, emtricitabine, elvitegravir and cobicistat appeared to be non-inferior to the comparator regimens (see Table). At baseline, 34–41% of patients had more than 100 000 HIV RNA copies/mL. After 48 weeks of treatment, concentrations had fallen to below 50 copies/mL in more than 80% of patients, regardless of whether they received the study drug or the comparator. This viral suppression was maintained after 96 weeks of treatment (see Table).[3,4] Increases in CD4 cell counts were comparable between treatments.[1-4]

During the first 48 weeks of the trials, 1.9% (13/701) of patients developed a resistance mutation to tenofovir, emtricitabine or elvitegravir. Most patients who were resistant to elvitegravir had cross-resistance to

‡ www.afao.org.au/about-hiv/the-hiv-epidemic/hiv-statistics-australia

Table **Efficacy of tenofovir, emtricitabine, elvitegravir and cobicistat compared to other combination antiretrovirals in patients with HIV** [1-4]

	Study 102		Study 103	
	Study drug	**Comparator**	**Study drug**	**Comparator**
Patient response§	tenofovir, emtricitabine, elvitegravir, cobicistat	tenofovir, emtricitabine, efavirenz	tenofovir, emtricitabine, elvitegravir, cobicistat	tenofovir, emtricitabine, atazanavir, ritonavir
at 48 weeks	87.6% (305/348 patients)	84.1% (296/352 patients)	89.5% (316/353 patients)	86.8% (308/355 patients)
at 96 weeks	84.2% (293/348 patients)	81.5% (287/352 patients)	83.3% (294/353 patients)	82.3% (292/355 patients)

§ patients with <50 RNA copies/mL

raltegravir. Some of these patients also had mutations associated with emtricitabine resistance.[1,2]

The most common adverse events of moderate severity in the 701 patients who received the study drug were diarrhoea (6%), headache (4%), upper respiratory tract infection (4%), bronchitis (4%), nausea (3%) and depression (3%). In the trials, 26 people discontinued – four because of proximal renal tubular injury.

The potential drug interactions with this product are numerous. Commonly used drugs that may interact include antacids, antibiotics, antifungals, antidepressants, antihistamines, beta blockers, methadone, phosphodiesterase-5 inhibitors, statins, oral contraceptives and St John's wort. Many of these drugs are contraindicated.

The recommended dose of this product is one tablet taken daily with food. Tenofovir and emtricitabine are excreted by the kidneys so treatment should only be started in patients with an estimated creatinine clearance of at least 70 mL/minute. Kidney function should be monitored and treatment stopped if this falls below 50 mL/minute.

This product is a pregnancy category B3 drug. Although there have been no data in humans, it was not teratogenic in animals and did not affect reproductive function. There is evidence however that some of the drugs in this product are excreted in milk and breastfeeding is not recommended.

This combination antiretroviral product seems to be non-inferior to currently available combination regimens for HIV treatment-naïve patients. It does not contain a non-nucleoside reverse transcriptase inhibitor and so may be beneficial for patients who are intolerant or resistant to this class of antiretroviral. However, it is associated with renal problems in some patients and renal monitoring is a requirement of treatment.

T T manufacturer provided additional useful information

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First published online 1 May 2014

Vorinostat

Approved indication: cutaneous T cell lymphoma
Zolinza (Merck Sharp & Dohme)
capsules containing 100 mg
Australian Medicines Handbook section 14.2.3

Cutaneous T cell lymphomas are non-Hodgkin lymphomas that occur in the skin but may involve lymph nodes, blood and visceral organs in more advanced disease. Most patients present with mycosis fungoides (patches, plaques, tumours or erythroderma) or Sézary syndrome (erythroderma with leukaemic involvement). There is no curative treatment, and goals for patients with advanced disease include preventing progression, inducing remission and improving their quality of life (for example relief from severe pruritus).

Vorinostat is an anticancer drug that inhibits histone deacetylases. Defective regulation of these enzymes has been identified in malignant cells, and restoring normal acetylation through inhibition may have an antitumour effect.

In an open-label phase II study, three dosing schedules of vorinostat were assessed in 33 patients who either had refractory disease or were intolerant of conventional treatments. Patients were assigned to doses of 400 mg once daily (group 1), 300 mg twice daily for three days a week (group 2), or 300 mg twice daily for two weeks followed by a week with no treatment then 200 mg twice daily (group 3). Response rates were assessed by calculating the percentage of total body surface area affected. Overall, eight patients (24%) had a partial response, defined as at least 50% reduction in skin involvement. No patients completely cleared their skin disease. Response rates were higher in groups 1 and 3, where patients received continuous treatment, compared to group 2 in which patients took vorinostat only three days a week (response rates: 31% and 33% vs 9%). Fourteen of the 31 patients with pruritus experienced symptomatic relief during the trial. Overall, the time to response varied between 3.6 and 21.9 weeks and the duration of response varied between 9.4 and 19.4 weeks. The median time to progression in the trial was 12.1 weeks.[1]

Serious adverse events occurred in 14 patients and included dehydration, thrombocytopenia, vomiting, anaemia, hypotension, infection, nausea, pulmonary embolism, fever and sepsis. The INR was increased in some patients on warfarin and decreased in others. Two patients died during the study – one as a consequence of disease progression and the other from untreated sepsis. Overall, the incidence of drug-related serious adverse events and discontinuations was lowest in patients who took vorinostat 400 mg once daily.[1]

In another non-randomised open-label phase II trial, 74 patients with advanced refractory disease received oral vorinostat 400 mg daily. Average treatment duration was 5.3 months. Overall 30% of patients partially responded to vorinostat. One patient was completely clear of skin disease after 281 days of treatment. Around a third of patients reported they had experienced relief from pruritus. The median time to response was 55 days (28 to 171 days). The median duration of response end point was not reached but was estimated to be at least 185 days (34 to 441 days). The overall time to progression was 148 days. Survival of patients was not reported.[2] At study completion, 58 of the 74 patients had discontinued treatment – 49 of these withdrawals were due to lack of efficacy or progressive disease and nine were due to an adverse event.

The most common drug-related adverse events in the trial were diarrhoea (48.6% of patients), fatigue (45.9%), nausea (43.2%), anorexia (25.7%), taste disturbance (24.3%), thrombocytopenia (21.6%), weight decrease (20.3%), alopecia (17.6%), muscle spasms (16.2%), blood creatinine increase (14.9%), anaemia (12.2%), chills (12.2%), vomiting (12.2%), constipation (10.8%) and dry mouth (10.8%). Most of these were mild to moderate, but some such as fatigue, thrombocytopenia, nausea, anorexia and muscle spasms were more severe. Drug-related serious adverse events occurred in eight of the 74 patients. These included pulmonary embolism, deep vein thrombosis, anaemia, blood creatinine increase, dehydration, gastrointestinal haemorrhage, ischaemic stroke, streptococcal bacteraemia, syncope and thrombocytopenia. There were three deaths in the trial – one from disease progression (day 52), one secondary to a stroke (day 227) and one of unknown cause (day 2).[2]

One of three patients taking warfarin in the trial required a dose reduction to maintain target INR. ECG changes were observed in 15 patients, including three patients with a prolonged QTc interval.[2]

As thromboembolic events have been reported with vorinostat, doctors should be vigilant for the signs and symptoms, particularly in patients with a history of pulmonary embolism and deep vein thrombosis. Dose-related thrombocytopenia and anaemia can also occur so platelet counts and haemoglobin should be monitored. Dose reduction or discontinuation of treatment may be needed. Prothrombin time and INR were altered in some patients taking warfarin with vorinostat and should be monitored closely.

Increased serum glucose was found in two-thirds of patients taking vorinostat. Transient increases in serum creatinine were also detected in almost half of patients. Occasionally these increases were severe. Fortnightly chemistry tests, including electrolytes, glucose and serum creatinine, are recommended for the first two months of treatment, then monthly after that.

Nausea, vomiting and diarrhoea are not uncommon with vorinostat. These can lead to dehydration and patients should be advised to drink at least 2 L water a day. Treatments for nausea, vomiting and diarrhoea may be required. Vorinostat should not be given with other drugs that inhibit histone deacetylases, for example valproic acid, as adverse effects may be cumulative. Severe thrombocytopenia with gastrointestinal bleeding and anaemia has been reported with concomitant valproic acid use.

Following an oral dose of 400 mg with a high-fat meal, peak serum concentrations of vorinostat were reached after a median of 4 hours (2–10 hours). Absorption is lower in the fasted state so vorinostat should be given with food. Vorinostat is extensively metabolised but only 1% of metabolites are excreted renally. It is contraindicated in severe hepatic impairment and is not recommended for people with moderate hepatic impairment.

Vorinostat seems to have some benefit for up to a third of patients given the 400 mg daily dose, either by reducing the amount of skin affected or relieving symptoms of pruritus. However, vorinostat is associated with serious adverse effects and it is not known if it actually extends the life of patients.[1,2]

Although vorinostat has been approved in the USA since 2006, an application for its approval in Europe was withdrawn by the sponsor in 2008. This appeared to be in response to queries from the European Medicines Agency (EMA), which was concerned that the trials were non-randomised and that there was no comparator to vorinostat. In the absence of a randomised controlled trial, it is difficult to quantify the risk of thromboembolism with vorinostat, and the EMA concluded that the risks may outweigh the benefits. They were also concerned that there were no survival data from the trials.

T manufacturer provided the AusPAR and the product information

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* 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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