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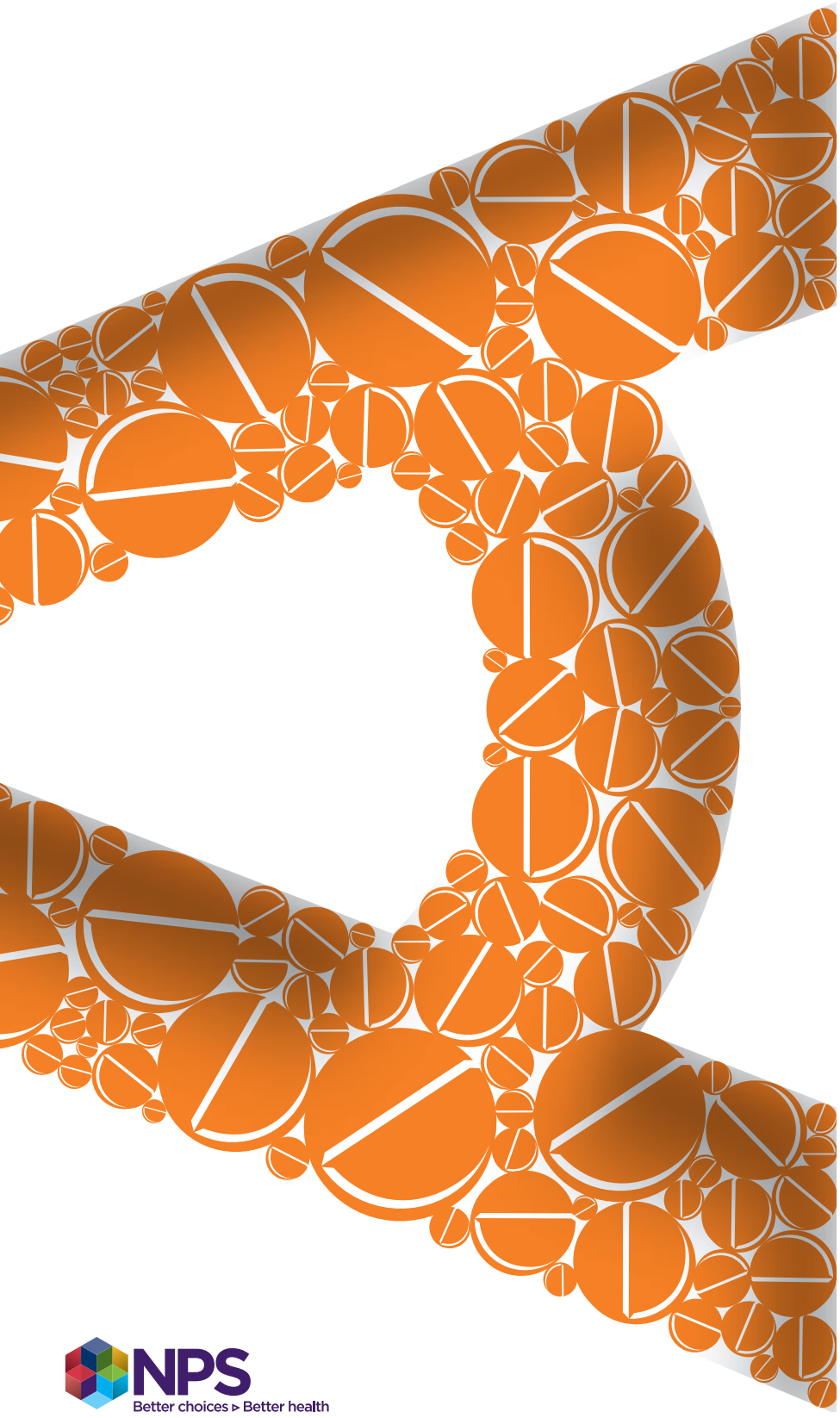

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EDITORIAL

Critical appraisal: court in the Act

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Australian Prescriber

Key words
advertising, complementary medicines, SensaSlim, drug regulation

Aust Prescr 2012;35:38–9

Freedom of expression may be under threat in Australia from companies using legal action, or the threat of it, to try and silence their critics. A recent case involves a health professional being sued for questioning the efficacy of a complementary medicine.

The product, SensaSlim, was said to be a combination of weight loss ingredients. Spraying it into the mouth was claimed to suppress appetite. Supporting evidence was said to come from 'the world's largest weight loss trial'. This was reported to have had 'sensational results' with 87% of the participants losing at least 10% of their body weight. Advertising for the product appeared in print and electronic media. Investors had the opportunity to buy franchises, reportedly for around $60 000 each.

In March 2011, Dr Ken Harvey complained about the promotion of the product to the Complaints Resolution Panel. This consists of members from the complementary medicines industry, advertising agencies, health professionals, consumers and government. It considers whether advertising has breached the Therapeutic Goods Advertising Code, the Therapeutic Goods Regulations or the Therapeutic Goods Act.[1]

The complaint gave a detailed analysis of the advertising claims and the lack of evidence to support them. As Dr Harvey had formed the opinion that the sensational results were most likely to have been fabricated, the complaint was also sent to the Therapeutic Goods Administration (TGA) and the Australian Competition and Consumer Commission (ACCC).

Shortly after these complaints were lodged, Dr Harvey was contacted by the company marketing SensaSlim. He was threatened with legal action if the complaint was not withdrawn. Similar pressure was applied to AusPharm, which had published information about the complaint on its website for pharmacists. AusPharm complied and withdrew the information, but Dr Harvey resisted the threat and within days a defamation action was launched in the Supreme Court of New South Wales. This claim sought damages of $800 000.[2]

The court action may have been intended to get the complaint withdrawn, but it also had the effect of silencing the Complaints Resolution Panel. An arcane regulation prevents the Panel from dealing with complaints about products which are the subject of court action. The litigation therefore enabled the company to continue promoting its product knowing that the Panel could do nothing while the action continued. Although it had been alleged that the advertising had breached the Therapeutic Goods Act, the TGA did not appear to be taking any action against the company.

While the legal process continued, questions began to be asked about the company. A doctor from the UK who had appeared in some of the company's promotional material withdrew his support. Investigative journalism then raised further questions. Pictures of the executives of the Intercontinental Research Institute, which supposedly carried out the trial, turned out to be photographs of American doctors who had no relationship with the company. Some of the pictures were also used on the website of an apparently non-existent Australian clinic called The Mountebank Clinic. This time the doctors were said to have Australian qualifications.[3] Given the dictionary definition*, would any doctor want to work at the Mountebank Clinic?

While the TGA appeared to be powerless, the ACCC considered that there may have been misleading and deceptive conduct by the company. The ACCC obtained a court order freezing the company's assets.[4] Around the same time, the company was placed into administration and a liquidator was subsequently appointed.

* mountebank: a swindler, a charlatan, a clown or an itinerant quack (Concise Oxford Dictionary)

From the Editor

Our approach to the treatment of asthma has changed. Helen Reddel explains why the focus is now on asthma control rather than severity.

Hypertension is another condition where treatment is adjusted to gain control. Peter Donovan discusses hypertension in pregnancy, while Julian Ayer and Gary Sholler consider childhood hypertension.

Children and adults with a history of anaphylaxis need to have immediate access to injectable adrenaline. Sandra Vale, Jill Smith and Richard Loh review the devices for autoinjection.

A new device for treating depression uses magnetic fields. Paul Fitzgerald describes the technology of repetitive transcranial magnetic stimulation.

Despite these developments, the TGA remained publicly silent and the defamation action against Dr Harvey continued. In August 2011 the case was dismissed in the Supreme Court of New South Wales. Although costs were awarded they are unlikely to be recovered from a company in liquidation. However, this was not the end of Dr Harvey's ordeal as the company's director launched a new defamation action in the Supreme Court of Queensland. This time damages of over $1 million were sought, but the case was eventually dismissed in February 2012.

The regulation of complementary medicines in Australia appears to be weak. The system should at least protect the public. Inaction in this case enabled false and misleading advertising to continue. The TGA may well have been working behind the scenes, but its strategy of silence and secrecy gave the appearance that it was doing nothing. The Complaints Resolution Panel had in fact recommended that the TGA consider cancelling the listing of SensaSlim on the Australian Register of Therapeutic Goods, but this did not occur until December 2011.

It is unacceptable that a health professional can face financial ruin for informing the government's medicines regulator that its rules are being broken. There may be dangerous precedents here. Could reporting adverse effects be potentially defamatory?

Could reporting adverse effects be potentially defamatory?

Clearly there needs to be some protection for people who make genuine complaints about medicines. As the TGA prefers a 'light touch' when regulating complementary medicines, there needs to be a robust and timely complaints procedure with effective sanctions. If the medicines industry does not want more regulation, then it too should take an active role in identifying and reporting rogue operators to the TGA. Otherwise complementary medicines could be seen as fertile ground for pushing placebos to enrich entrepreneurs, charlatans and crooks. <

Conflict of interest: none declared

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Letters to the Editor

Medicines labelling

Editor, – I have major concerns about Ropivacaine Sandoz, which has appeared in several private hospitals.

This product is labelled ropivacaine 150 mg/20 mL. Nowhere on the packet or the ampoule does it say that this is equivalent to 0.75% ropivacaine, or 7.5 mg/mL. When ropivacaine was first marketed about ten years ago it was marketed as 2 mg/mL, 7.5 mg/mL or 10 mg/mL strengths. More recently this was changed to percent labelling (0.2%, 0.75% and 1%) to make it consistent with all the other available local anaesthetics.

My concern is that nowhere on the packaging does it say that this is 0.75% ropivacaine or 7.5 mg/mL. It only has the total amount of milligrams in the bottle. This is a great potential source of confusion and particularly if ropivacaine is being used on the ward. Many nurses have expressed to me their confusion when looking for the requested local anaesthetic.

I think the labelling is inadequate and unsafe. It is clearly a potential source of medication error.

Paul Herreen
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Editor, – There are two aspects of prescriptions that can cause problems to patients, pharmacy staff and doctors.

Firstly, repeat authorisation forms are confusing – all the information is there, but there are three boxes

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

LETTERS

of information for the patient. Number of repeats remaining is sometimes not interpreted correctly, perhaps because the 'Number of supplies left' line is overshadowed by the bar code and the patient only reads the information in the two boxes above.

Patients ask for a repeat prescription when there is still one repeat outstanding, or are occasionally directed by pharmacy staff to ask for a repeat. If the form was altered so that it stated (1) the original prescription details – and put in the total number authorised (not just repeats), and (2) the number of supplies left – and leave the space for the bar code free, I think there would be no confusion.

Secondly it is frustrating, and potentially dangerous for patients that the highlighted name on dispensed medications and the repeat prescription is the trade name, with the generic name in smaller print.

We used to know the trade names, but now there are so many it is impossible to know them all. For prescribers, it is a time consuming process to try to work out what is being requested – and the worst situation by far is the Webster pack system. It is dangerous for patients. For example, recently a patient was taking the same medication twice because of different trade names.

It would be safer and so much more logical if the large print name was the generic name and the trade name was in smaller print.

John Jackson
General practitioner
Ipswich, Qld

Daniel Lalor, author of the article 'Medicines labelling' (Aust Prescr 2011;34:136-8), comments:

Drs Herreen and Jackson provide some excellent examples of how medicines labelling and packaging can be detrimental to the quality use of medicines.

Dr Herreen has demonstrated to us the difficulties that health professionals have when product strength is expressed in a non-standardised way. The use of ratios and percentages to express the strength of a medicine has long been known to cause confusion. Doctors make considerably more calculation errors when concentrations are expressed as ratios or percentages rather than as milligrams per millilitre (mg/mL).[1,2]

Simulation studies have shown that expressing a dose as concentration (mg/mL), quantity (total mg in packaging) and volume (total volume in packaging) can improve safety.[3] Standardising the way in which strength is presented should be strongly considered as a mechanism to improve safety.

I firmly support Dr Jackson's call for an increased prominence of the active ingredient on all medicines labelling, as do many consumers and other healthcare professionals. Standardising the prominence and position of medicines names on manufacturers' labelling as well as pharmacy applied labels, would also assist consumers in identifying their medicines and prevent medication misadventure.

These issues, and others, must be considered as part of the current Therapeutic Goods Administration medicines labelling review process.

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Lanthanum carbonate

Editor, – Shire Australia wishes to update the information about lanthanum carbonate that was published when the drug was new (New drugs, Aust Prescr 2006;29:54-5). Much has changed over the last six years and many more studies have been published, including long-term studies and a head-to-head comparison with sevelamer hydrochloride.

Given the current body of evidence, there appears no reason to suggest that lanthanum carbonate should not be used beyond two years. In fact, the Therapeutic Goods Administration considered the body of evidence in 2007 and made a decision to remove the two-year restriction. Treatment of patients for up to six years has not shown change in the harm–benefit profile.

Lanthanum carbonate is an effective binder of dietary phosphate for use in controlling the hyperphosphataemia of patients with chronic kidney disease on dialysis. Studies have shown that lanthanum carbonate can reliably be used to reduce serum phosphate concentrations and to effectively maintain control of serum phosphate during long-term use, up to six years.[1,2] Maintenance of target phosphate concentrations has been shown to be similar between lanthanum, calcium phosphate binders[1] and sevelamer hydrochloride.[3]

To date, 6297 patients have been exposed to lanthanum carbonate in Shire-sponsored clinical studies. In addition 5020 patients have been exposed for up to five years in two observational studies. Cumulatively the estimated worldwide patient exposure to lanthanum is 225 224 person-years treatment. The most commonly reported adverse drug reactions are headache, hypocalcaemia and gastrointestinal reactions (for example abdominal pain, diarrhoea, nausea and vomiting). Gastrointestinal reactions can be minimised by taking the tablets with food.

Results from long-term studies demonstrated that bone lanthanum concentration had no apparent effect on bone health (assessment has considered bone biopsy) or treatment outcome for up to 4.5 years.[1] There are no clinical data examining the potential deposition of lanthanum in other tissues.

Beata Niechoda
Medical Director
Shire Australia
Sydney

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New drugs for osteoporosis

Editor, – Professor Ebeling's article (Aust Prescr 2011;34:176-81) provided a succinct summary of the current available pharmacological interventions for osteoporosis.

However, with regard to Pharmaceutical Benefits Scheme-listed indications for osteoporosis drugs (Table of the article), alendronate is now indicated for patients (aged 70 or older) with a T-score of –2.5 or less (www.pbs.gov.au/medicine/item/8511Y).

Kevin Kwan
Registrar, Geriatric medicine
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Professor Peter Ebeling, author of the article, comments:

I thank Dr Kwan for the additional information. This was not available when the article was finalised for publication.

Thromboprophylaxis and elective surgery

Editor, – Thank you for the informative and detailed article on antiplatelets, anticoagulants and elective surgery (Aust Prescr 2011;34:139-43).

The authors noted that patients requiring a biopsy during an elective endoscopy should follow the recommendations for those having general surgery. However, patients who do not require a biopsy during an endoscopy should follow the recommendations for dental, dermatological and ophthalmological procedures. In practice, it is usually not known before a colonoscopy whether or not a polypectomy will be required, and some gastroenterologists perform biopsies on most or all patients having elective endoscopies. I therefore presume the take-home message is to treat most patients according to the recommendations applying to general surgery.

I was also interested to read that warfarin could be resumed on the evening of the procedure, but at the usual maintenance dose with no loading dose. Why is a loading dose not advised? Having a patient at a sub-therapeutic INR level for a relatively prolonged period after a procedure can complicate the logistics of their care, particularly if they are unable or unwilling to self-administer low molecular weight heparin, and live in a rural area.

Kylie Fardell
General practitioner
Cooma, NSW

Dr Merriman and Dr Tran, authors of the article, comment:

Thank you for your comment on our article. You are correct – if it is likely that a biopsy is to be taken or a polyp removed during an endoscopic procedure, then we would advise following the recommendations for general surgery.

When resuming warfarin after such procedures, for atrial fibrillation one would usually commence this at the usual maintenance dose as these patients are not generally loaded with higher doses even when first started on warfarin. For patients at higher risk, such as atrial fibrillation with prior thrombosis, mechanical heart valves or previous deep vein thrombosis or pulmonary embolism, one could start with a higher loading dose using a warfarin nomogram and bridge with low molecular weight heparin as per our guideline.

LETTERS

Atrial fibrillation

Editor, – We read with interest the article 'Current management of atrial fibrillation' (Aust Prescr 2011;34:100-4). We commend the authors for their comprehensive overview of the topic and for presenting some pertinent issues relating to atrial fibrillation and stroke medicine.

From a stroke perspective, atrial fibrillation is not only a major risk factor for future stroke – it is an independent predictive factor for severe stroke and early death in patients with acute ischaemic infarction.[1] Data from a large Japanese stroke registry demonstrated that acute ischaemic stroke severity was significantly higher in patients with atrial fibrillation compared to those without atrial fibrillation (median National Institutes of Health Stroke Scale score 12 vs 5, p<0.0001). Mortality rate within 28 days from admission was also higher in patients with atrial fibrillation than for those without atrial fibrillation (11.3% vs 3.4%, p<0.0001).

It is important to emphasise that transient ischaemic attacks contribute two points to $CHADS_2$ scoring, and so even in the absence of any other $CHADS_2$ risk factors, a transient ischaemic attack is a compelling reason to commence anticoagulation in a patient with atrial fibrillation.

It is significant to note that a history of falls is not a component of the HASBLED score. Clinicians commonly elect not to commence warfarin if the patient has a history of falls. The evidence supporting this clinical decision is lacking. In patients with atrial fibrillation and at risk of falls, the data suggest that stroke risk reduction with anticoagulation outweighs haemorrhage risk.[2]

The new oral inhibitors of thrombin and factor Xa have other limitations, including adherence and the lack of a test of anticoagulant activity.[3] It remains to be seen how these drugs will affect thrombolysis decisions. An absolute contraindication to thrombolysis may have to apply to any patient thought to be taking dabigatran, due to the inability to quantify its anticoagulant effects and the unknown risk associated with thrombolysis in patients on dabigatran therapy.

Doron Hickey
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Benjamin Tsang
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Dr Himabindu Samardhi, Dr Maria Santos, Dr Russell Denman, Dr Darren Walters and Dr Nick Bett, authors of the article, comment:

We thank Doron Hickey and Benjamin Tsang for their comments and agree that there is no simple overall protocol for managing patients with atrial fibrillation and a history of falls. Their individual risks have to be assessed[1] and weighed against the risk of stroke.

We are also concerned because of the lack of tests of anticoagulant activity and adherence[2] for patients taking factor Xa and direct thrombin inhibitors, and because drugs to reverse their effects are not routinely available.[3,4] There is insufficient information about the risks of administering thrombolysis, unfractionated heparin, enoxaparin or glycoprotein IIb/IIIa inhibitors such as abciximab to patients on these drugs.

Since our article appeared, trials of factor Xa inhibitors for atrial fibrillation have been published.[5,6] Further studies will be required to compare the efficacy and safety of these drugs and direct thrombin inhibitors, especially in those with renal impairment.

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ARTICLE

Rational prescribing for ongoing management of asthma in adults

SUMMARY

Although asthma is one of the most common chronic conditions in Australia, current treatment often fails to reflect clinical practice guidelines.

Improving the patient's management first requires an assessment of how well their asthma is controlled.

Factors such as poor inhaler technique and poor adherence may contribute to poor asthma control. These need to be addressed before adjusting the patient's drug prescription.

Simple processes for step-up and step-down adjustments of treatment are used to maintain good control while minimising adverse effects.

There should be an emphasis on shared decision-making to improve patient understanding and acceptance of treatment.

Introduction

Deaths from asthma have dramatically fallen in recent years, so asthma is now often perceived as a commonplace and rarely serious condition. However, treatment of asthma in Australia is not optimal. The majority of preventer prescriptions for asthma in adults (≥15 years) are for the highest potency combination of an inhaled corticosteroid and long-acting beta$_2$ agonist rather than a low-dose inhaled corticosteroid (≤400 microgram/day budesonide or equivalent) which alone should be sufficient for most patients.[1,2] In addition, more than half of the people aged 15–34 years are dispensed these medications only once in a year. Most patients use their inhalers incorrectly, and only 22% of patients have a written asthma action plan.[1]

Clinical outcomes and costs could be substantially improved if an evidence-based approach was taken to tailoring an individual's asthma assessment and management.

Identifying the need for treatment – how to assess asthma control

Current asthma guidelines are based on assessment of the patient's level of asthma control. This is the extent to which the effects of asthma have been reduced or removed by treatment.[3] There are two important components.

The first component is the level of **current control**. This is determined by the frequency of symptoms, use of reliever inhalers and activity limitation over the last month, and spirometry. Simple assessment tools include the Asthma Score*, and the Global Initiative for Asthma (GINA) categorisation (controlled, partly controlled or uncontrolled).[2] The level of control should be recorded at each visit to facilitate comparison. Sub-optimal current control is indicated by an Asthma Score <20, symptoms or reliever use three or more times per week, or any night waking from asthma.

The second component of asthma control is the patient's **future risk** of adverse outcomes, particularly exacerbations and adverse drug reactions. This may appear unnecessary, since patients with well-controlled symptoms generally have few exacerbations, and uncontrolled symptoms should prompt treatment review. However, additional risk factors for patients with few current symptoms are one or more exacerbations in the past year, any intensive care unit admission for asthma, low lung function, smoking, and long-term use of high-dose inhaled corticosteroids.[3]

Asthma control is the extent to which the effects of asthma have been reduced or removed by treatment

Why focus on asthma control rather than severity?

In many chronic diseases, treatment is based on the initial disease severity, an intrinsic and relatively static feature. Previously, asthma 'severity' was based on the initial clinical features. However, patients with similar symptoms had widely differing responses to treatment. Asthma is now perceived as a syndrome with several underlying pathophysiological processes which are variably modified by inhaled corticosteroid treatment.

Asthma severity is now defined by the level of treatment required to achieve best asthma control.[3] 'Mild asthma' can be well controlled on low-dose inhaled corticosteroids, but 'severe asthma' requires high-dose combination therapy or is uncontrolled despite such treatment.

* www.asthmascore.com.au

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Key words
beta agonists, exacerbations, glucocorticoids

Aust Prescr 2012;35:43–6

When asthma is not well controlled

Once or twice a year each patient's asthma control and risk factors should be reviewed, and treatment adjusted if necessary. Patients may also make short-term adjustments for worsening asthma in accordance with their written action plan.

In general, clinical guidelines recommend that patients experiencing symptoms three or more times a week or with one or more exacerbations per year should commence regular low-dose inhaled corticosteroids, or step up their existing preventer treatment. However, before any step-up, some important factors should be considered.

Are the symptoms due to asthma?

Asthma symptoms are non-specific, and new symptoms may be due to other conditions such as rhinitis, cardiac failure or vocal cord dysfunction.[4]

Is inhaler technique correct?

Most patients and health professionals have incorrect inhaler technique, but are unaware of this.[5] The only way to identify incorrect technique is to watch the patient using their inhaler.*

Most patients and health professionals have incorrect inhaler technique, but are unaware of this

The inhaler device should not be changed simply because the patient's technique is incorrect. Education about inhaler technique takes only 2–3 minutes, but is often very effective in improving asthma control[6] and is valued by patients. A physical demonstration, either in person or by video, is essential to improve inhaler technique.[7] Checklists and videos are available on the National Asthma Council website.[5,8]

Question adherence

Patients are often reluctant to admit to poor adherence. Permissive wording can assist, for example, 'Would you usually take your inhaler once or twice a week, or less, or more?'. Poor adherence should not be surprising in asthma, with intermittent symptoms that usually respond rapidly to a reliever inhaler. In Australia, these medications are cheaper and more readily available than preventer medications, and patients often perceive them as safer.

Poor adherence may be classified as either intentional – where the patient makes a reasoned choice that the drug's perceived risks outweigh its perceived benefits – or unintentional, due to forgetfulness[9] or cost[10].

There are few easy solutions to poor adherence. For unintentional poor adherence, suggest an alarm, placing the inhaler next to the toothbrush, or simplifying the medication regimen. Cost may be an issue, even for patients with a concession card.[10] In this situation, consider the relative cost to the patient of different preventer options, and aim for regular daily use even if at a low dose. For intentional poor adherence, a discussion about perceived risks and benefits can identify key barriers. An agreed dose can be negotiated using shared decision-making and goal-setting strategies, with little increase in consultation times.

Other factors?

Before increasing treatment, consider if poor control is due to rhinosinusitis, smoking, occupational exposure, allergens or drugs such as beta blockers. For many triggers, reducing exposure is beneficial, but evidence for house dust mite avoidance strategies is limited. Breathing exercises can help to reduce anxiety-related symptoms or reliever overuse, but they do not improve lung function or airway inflammation.[11]

Consider a therapeutic trial of step-up treatment

Consider a dose increase or add-on therapy only after dealing with other factors contributing to poor control. Handle any change as a therapeutic trial, and document the patient's level of asthma control before and after the change. Set a review date, for example 2–3 months, and agree on criteria for assessing the patient's response.[3]

Step-up options

For patients whose asthma is uncontrolled on low-dose inhaled corticosteroids, two different step-up regimens are available. One option is a conventional regimen of low-dose inhaled corticosteroid with a long-acting $beta_2$ agonist, with a short-acting $beta_2$ agonist for symptom relief. Currently, the Pharmaceutical Benefits Scheme requires that patients should first be stabilised on separate inhalers, rather than a combination inhaler. However, this requires an additional visit and may increase the chance that patients will only take the long-acting $beta_2$ agonist.

The other step-up is a combination of low-dose budesonide and eformoterol (100/6 or 200/6), used as both maintenance and reliever therapy. This is possible because budesonide/eformoterol has a similar onset of action to salbutamol. With this regimen, levels of asthma control are similar and the risk of exacerbations is reduced or similar, versus higher-dose inhaled corticosteroid or inhaled corticosteroid/long-acting $beta_2$ agonist.[12] This apparent paradox is

* See 'Common problems with inhaler devices' with this article online at www.australianprescriber.com/magazine/35/2/43/6

probably explained by the more timely, albeit small, increase in anti-inflammatory and bronchodilator dose as soon as symptoms worsen. This regimen reduces the risk of adverse effects, but is not suitable for patients who habitually overuse short-acting $beta_2$ agonists, who poorly perceive airway obstruction, or who would be confused by a regimen change.

If further step-up treatment is required, moderate or high-dose combination therapy can be used, but long-term adverse effects should be considered. A few patients remain uncontrolled and should be referred for consideration of other add-on therapy.

When asthma is well controlled

Once symptoms are stable for three months and exacerbations are infrequent, step-down should be actively initiated in order to minimise the risk of adverse effects, such as osteoporosis and cataract. Clinicians may be concerned about destabilising previously well patients, but this may result in over-prescribing, and reinforce patient concerns about high doses. It is helpful to explain that both the overall dose and risk of exacerbations can be lowered by gradually decreasing to a low, regular, daily dose, rather than by stopping and starting treatment.

How to step down

Maintenance treatment can be gradually reduced at intervals of around two months, with inhaled corticosteroid dose reduced by 25–50% each time. Each change should be treated as a therapeutic trial, with the level of asthma control documented. There are few studies on which to base recommendations, but it would be reasonable to check lung function after the dose of inhaled corticosteroid has been reduced by 50%, or more frequently for patients who are anxious or at greater risk. Patients should be advised to return to the previous dose or medication and contact the doctor if their asthma is consistently worse after a step-down.

For patients taking conventional fixed-dose combination therapy, step down through the available formulations. This reduces the inhaled corticosteroid dose by around 50% each time, mostly without changing the dose of long-acting $beta_2$ agonist. For patients taking the budesonide/eformoterol combination as maintenance and reliever therapy, the maintenance dose can be reduced, with the as-needed doses providing an immediate safety net if the patient's control deteriorates.

Once the lowest dose of combination therapy has been reached, options are to shift to once-daily dosing, which can be an effective option when the inhaled corticosteroid dose is ≤400 microgram daily, or to withdraw the long-acting $beta_2$ agonist and treat with inhaled corticosteroid alone.[13]

Conclusion

Stepping-up and stepping-down treatment for asthma is not substantially different from the treatment principles for hypertension or diabetes. Assess the patient's status, prescribe an appropriate starting medication, ensure that the patient knows how and when to take it, review the patient's response, then monitor and readjust the treatment over subsequent visits. Inhaler technique and adherence should be assessed at every visit. ◅

Associate Professor Reddel has served on advisory boards for AstraZeneca, GlaxoSmithKline and Novartis, has provided consulting for Biota, GlaxoSmithKline and Novartis. She has received honoraria from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline for educational presentations, is chairing a joint data monitoring committee for AstraZeneca, GlaxoSmithKline, Merck and Novartis, and has received research funding from AstraZeneca and GlaxoSmithKline.

Note: The June issue will feature an article on written asthma plans.

Q:

SELF-TEST QUESTIONS

True or false?

1. The severity of a patient's asthma is determined by their symptoms and lung function at the time of diagnosis.
2. Patients with newly diagnosed asthma should start treatment with a combination inhaler containing a corticosteroid and a long-acting $beta_2$ agonist.

Answers on page 71

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Your questions to the PBAC

Methotrexate

We would like to suggest a simple measure to reduce the risk of potentially life-threatening adverse effects associated with unintentional overdose of methotrexate. This problem has been highlighted in the past, with recommendations for clear labelling and patient counselling to minimise the risk.[1] Labels should name the specific weekday for dosing. The instruction to 'take as directed' is unacceptable.

Despite these measures, we continue to see patients suffering severe adverse effects because they have taken methotrexate daily instead of weekly as prescribed. These patients are often elderly and particularly susceptible to poor outcomes.

Maximum quantities of methotrexate allowed on the Pharmaceutical Benefits Scheme (PBS) are 30 and 15, for 2.5 mg and 10 mg tablets respectively. For a patient on a weekly dose of 15 mg, up to 15 weeks treatment can be dispensed at one time. Consequently, inappropriate daily use can continue for two weeks before a repeat is requested and there is an opportunity to spot the error.

If prescribers restrict the quantity of methotrexate ordered to a maximum of four weeks supply, as with most other PBS items, unintentional overdose could effectively be limited to just four days before repeat supply would have to be obtained. If pharmacists are alert for early requests for repeat supplies, this simple measure would greatly increase the chances of the patient error being noticed by a health professional, and potentially reduce the adverse consequences of such an error.

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The Pharmaceutical Benefits Advisory Committee responds:

Although a maximum quantity is set out in the Schedule of Pharmaceutical Benefits, there is flexibility to vary the quantity prescribed for those patients taking doses that are higher or lower than usual. It is the responsibility of the doctor to ensure that individual patients are prescribed the quantity which is most suitable for their needs.

If a prescriber believes a lesser quantity is sufficient for the patient's needs, then a quantity less than the listed maximum quantity may be prescribed and dispensed. Under the PBS, an allowance is paid to pharmacists for dispensing a lesser quantity from a standard pack.

At its March 2008 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended the unrestricted listing of methotrexate 10 mg, in a smaller 15 tablet pack size. As a consequence, the PBAC also recommended a restricted benefit listing for the methotrexate 10 mg, 50 tablet pack size, limiting use to patients requiring a dose of more than 20 mg per week. The unrestricted benefit listing for methotrexate 2.5 mg remained unchanged.

ARTICLE

Hypertensive disorders of pregnancy

SUMMARY

Hypertensive disorders of pregnancy are common and represent a spectrum of disease ranging from chronic and gestational hypertension to eclampsia. They are associated with increased risk of both adverse maternal and fetal outcomes.

Drug treatment is generally reserved for moderate or severe hypertension. Pre-eclampsia–eclampsia can be life-threatening and requires urgent investigation and intervention. There are limited data about the safety of many hypertensive drugs in pregnancy. ACE inhibitors and angiotensin receptor blockers should be avoided.

Women who have had any hypertensive disorder in pregnancy have an increased cardiovascular risk. They require long-term follow-up.

Introduction

Hypertensive disorders affect 10–22% of pregnancies and have been classified into four conditions, reflecting potential differences in aetiology and pregnancy outcomes:[1,2]

- chronic hypertension
- gestational hypertension
- pre-eclampsia–eclampsia
- pre-eclampsia superimposed on chronic hypertension.

The incidence of these disorders is not entirely clear, but pre-eclampsia is thought to affect 5–8% of pregnancies. Chronic hypertension accounts for approximately 20% of the cases of high blood pressure seen in pregnancy.[1,3]

Chronic hypertension

Chronic hypertension is diagnosed when hypertension is confirmed before pregnancy or before 20 weeks gestation (blood pressure >140 mmHg systolic and/or >90 mmHg diastolic).[3] However, chronic hypertension is frequently diagnosed when high blood pressure fails to resolve post-partum. Women with chronic hypertension require careful monitoring during pregnancy as they have an increased risk of adverse events, including superimposed pre-eclampsia, placental abruption, fetal growth restriction, premature delivery and stillbirth.[3]

Pre-pregnancy counselling and management of chronic hypertension is essential. Some commonly prescribed antihypertensive drugs are contraindicated or best avoided before conception and during pregnancy (Table 1). These include ACE inhibitors, angiotensin receptor antagonists, diuretics and most beta blockers.[3,4]

Where indicated, it is advisable to look for secondary causes of hypertension before conception, as normal physiological changes in pregnancy can make many of these screening tests difficult to interpret. If this is not possible, with the exception of phaeochromocytoma, further investigation is often best deferred until the postpartum period. In all cases, preconception assessment for proteinuria (with urine protein:creatinine ratio) is recommended as a baseline measurement.

Treatment

With the exception of acute, severe hypertension, treatment with antihypertensive drugs during pregnancy remains controversial. In many cases, the

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Key words
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Table 1 **Antihypertensive drugs to avoid in pregnancy and preconception**

ANTIHYPERTENSIVE	ADVICE	POTENTIAL ADVERSE EVENTS
ACE inhibitors	Contraindicated	Teratogenic in first trimester Fetal renal dysfunction, oligohydramnios and skull hypoplasia in second and third trimesters
Angiotensin receptor blockers	Contraindicated	Teratogenic in first trimester Fetal renal dysfunction and oligohydramnios in second and third trimester
Diuretics	Avoid	Fetal electrolyte disturbances, reduction in maternal blood volume
Beta blockers (except labetalol and oxprenolol)	Avoid	Fetal bradycardia, long-term use of atenolol associated with fetal growth restriction
Calcium channel antagonist (except nifedipine)	Avoid	Maternal hypotension and fetal hypoxia

physiological fall in blood pressure that occurs during the first trimester leads to normalisation without the need for medication. There is no direct evidence that continued treatment of chronic hypertension leads to a reduction in the risk of adverse pregnancy events.[3] Benefits appear to be confined to reducing severe hypertension (≥170/110 mmHg), however most centres start or continue antihypertensive drugs when blood pressure exceeds 160 mmHg systolic and/or 100 mmHg diastolic on more than one occasion.[3] Table 2 outlines the antihypertensive drugs most commonly used in pregnancy.[3,4]

Blood pressure reduction to 140–160 mmHg systolic and 90–100 mmHg diastolic are acceptable treatment goals. Stricter blood pressure control may be associated with fetal growth restriction, presumed to be related to relative placental hypoperfusion. Importantly, women need to be carefully monitored for any signs of pre-eclampsia which may include worsening hypertension and new or worsening proteinuria (see Box). Repeated assessment of fetal wellbeing and growth is appropriate, although given that there are no guidelines, the frequency of monitoring is usually at the discretion of the woman's treating obstetrician.

Gestational hypertension

Gestational hypertension is defined as:

- new onset of hypertension after 20 weeks gestation
- no other features to suggest pre-eclampsia (see Box)
- normalisation of blood pressure within three months postpartum.

Gestational hypertension is associated with adverse pregnancy outcomes. These are more common if it presents earlier in the pregnancy, if it progresses to pre-eclampsia or if hypertension is severe (≥170/110 mmHg).[3]

Although rare, phaeochromocytoma can initially present in pregnancy. It can be fatal. Investigation is needed if there are any other features to suggest a phaeochromocytoma (for example paroxysmal hypertension, episodic headache and sweating), or if the onset of hypertension occurs early in the pregnancy or is severe. Plasma or urinary metanephrines (catecholamine metabolites) tend not be affected by the physiological changes of pregnancy and are useful as screening investigations.[5]

The benefits of treating mild to moderate hypertension are limited to the prevention of severe hypertension and appear to have no effect on the potential for adverse pregnancy outcomes. The indications for treatment with antihypertensive drugs, goals of therapy and the choice of drug are similar to the treatment of chronic hypertension in pregnancy (Table 2). Up to 25% of women who develop hypertension in pregnancy will eventually be diagnosed with pre-eclampsia, even if no other manifestations are present initially. Regular monitoring of blood pressure, and investigation for proteinuria and other features of pre-eclampsia (up to once or twice per week) is reasonable.[3]

By definition, gestational hypertension should resolve within three months postpartum and the patient can generally be weaned off antihypertensive drugs within weeks. If hypertension has not resolved within three months, an alternative diagnosis – for example chronic (essential or potentially secondary) hypertension – needs to be considered. There is a risk of recurrence in subsequent pregnancies so increased monitoring will be required.

Pre-eclampsia, eclampsia and superimposed pre-eclampsia

The aetiology of pre-eclampsia is unclear although a combination of maternal and placental factors are likely to contribute. Abnormal placental formation, resulting in aberrant angiogenic factor production and systemic endothelial dysfunction, as well as genetic and immunological factors, are thought to play a role. Risk factors include nulliparity, age less than 18 or more than 40 years, a past history of pre-eclampsia and maternal medical comorbidities (hypertension, diabetes mellitus, renal disease, obesity, antiphospholipid antibodies or other thrombophilia and connective tissue disease).[6] Pre-eclampsia is associated with fetal growth restriction, preterm delivery, placental abruption and

Box **Features of pre-eclampsia**

Hypertension with onset after 20 weeks gestation
Renal manifestations
Significant proteinuria
Serum creatinine >90 micromol/L (or renal failure)
Oliguria
Haematological manifestations
Disseminated intravascular coagulation
Thrombocytopenia
Haemolysis
Hepatic manifestations
Raised serum transaminases
Severe right upper quadrant or epigastric pain
Neurological manifestations
Eclamptic seizure
Hyperreflexia with sustained clonus
Severe headache
Persistent visual disturbances
Stroke
Pulmonary oedema
Fetal growth restriction
Placental abruption

perinatal death.[7] Severe pre-eclampsia has the potential for progression to eclampsia, multi-organ failure, severe haemorrhage and rarely maternal mortality.

Pre-eclampsia is a disorder with many manifestations. New onset hypertension after 20 weeks gestation and proteinuria are the most common presenting features. A urine dipstick for proteinuria can be a useful screening test, but is confounded by high false positive and false negative rates. If there is any uncertainty, assessment of the urine protein:creatinine ratio is advised. Peripheral oedema is no longer considered a diagnostic feature of pre-eclampsia as it is neither a sensitive nor specific sign. Other clinical manifestations are outlined in the Box, with their presence suggesting severe pre-eclampsia.

The presence of severe pre-eclampsia mandates urgent review. A multidisciplinary team approach (obstetrician, midwife, neonatologist, anaesthetist and physician) is often required. Delivery is the only definitive management for pre-eclampsia. The timing of delivery is dependent on the gestational age and well-being of the fetus and the severity of the pre-eclampsia. The pregnancy is rarely allowed to go to term. Management of pre-eclampsia before 32 weeks gestation should occur in specialist centres with sufficient expertise and experience. Severe hypertension may require parenteral antihypertensive drugs (such as hydralazine), which should only be given in a suitably monitored environment (birth suite or high dependency unit). Intravenous magnesium sulfate is given for the prevention of eclampsia in severe cases.[8]

Although pre-eclampsia progressively worsens while the pregnancy continues, outpatient management may be considered in selected cases. The antihypertensive drugs used in pre-eclampsia are the same as those used to treat chronic and gestational hypertension (Table 2).[3] The treatment goals for blood pressure control are also the same (140–160 mmHg systolic and 90–100 mmHg diastolic). Although widely advised in the past, there is little evidence to support bed rest. Given the potential for venous thromboembolism from immobilisation, bed rest is generally only advised with severe, uncontrolled hypertension.[9]

Postpartum management and secondary prevention

Most of the manifestations of pre-eclampsia resolve within the first few days or weeks postpartum. The features of pre-eclampsia, including hypertension, may worsen before they improve. Rarely the first manifestations occur postpartum. Frequent review of blood pressure during this period is essential, for example once to twice weekly. Antihypertensive doses are reduced or ceased when the blood pressure falls to less than 140/90 mmHg. Home blood pressure monitoring with an automated device can be helpful to avoid hypotension. This is a common occurrence, as the features of pre-eclampsia and therefore antihypertensive requirements can recede precipitously. Like gestational hypertension, if the blood pressure does not normalise within three months consider an alternative diagnosis. It is also important to confirm that proteinuria has resolved.

Pre-eclampsia can recur in subsequent pregnancies with the most prominent risk factors being previous severe or early onset pre-eclampsia or chronic hypertension. The use of low-dose aspirin has been shown to be safe and beneficial in decreasing this risk in women with a moderate to high risk of pre-eclampsia. Aspirin is therefore generally advised in subsequent pregnancies. It is started at the end of the first trimester and can be safely continued until the third trimester, with most centres ceasing therapy at 37 weeks gestation. Calcium supplements (1.5 g/day) may be of benefit, particularly in women at risk for low dietary calcium intake. The administration of vitamin C and E supplements has not been shown to be beneficial and may be harmful.[3]

Table 2 **Relatively safe antihypertensive drugs in pregnancy**

ANTIHYPERTENSIVE	CLASS	STARTING DOSE	MAXIMUM DOSE	IMPORTANT ADVERSE EFFECTS
Labetalol	Beta blocker	100–200 mg twice a day	400 mg three times a day	Bradycardia, bronchospasm, transient scalp tingling
Oxprenolol	Beta blocker	40–80 mg twice daily	80–160 mg twice daily	Bradycardia, bronchospasm
Nifedipine	Calcium channel antagonist	10 mg twice a day, 30 mg daily controlled release	20–40 mg twice a day, 120 mg daily controlled release	Severe headache, peripheral oedema
Methyldopa	Centrally-acting	250 mg twice a day	500 mg four times a day	Sedation, light-headedness, dry mouth, nasal congestion, haemolytic anaemia, depression
Hydralazine	Vasodilator	25 mg twice a day	50–200 mg total daily dose	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day	3 mg total daily dose	Postural hypotension

Antihypertensive drugs postpartum

The choice of antihypertensive drugs depends on whether breastfeeding is attempted. When the woman wishes to breastfeed, consideration must be given to potential transfer of the drug into breast milk. Most drugs safely used in pregnancy are excreted in low amounts into breast milk and are compatible with breastfeeding. Table 3 shows antihypertensive drugs to use or avoid during lactation.[4] Should there be no desire to breastfeed and adequate contraception is used, the choice of antihypertensive drug is the same as for any other non-pregnant patient.

Long-term follow-up

Pre-eclampsia and gestational hypertension appear to be associated with an increased long-term risk of cardiovascular disease, including hypertension, ischaemic heart disease, stroke and venous thromboembolism.[10] There may also be a small increased risk of chronic renal failure and thyroid dysfunction after pre-eclampsia.[11,12] Annual assessments of blood pressure and at least five-yearly assessments for other cardiovascular risk factors are advisable.[3] Thyroid and renal function should also be measured intermittently.

Conclusion

Pregnancies affected by hypertensive disorders require careful monitoring due to the increased risks of adverse pregnancy outcomes. New onset hypertension in pregnancy warrants consideration of pre-eclampsia. Antihypertensive drugs for all forms of hypertensive disorder of pregnancy tend to be reserved for persistent or severe hypertension. Many standard antihypertensive drugs are contraindicated in pregnancy and lactation. In women at moderate to high risk for recurrent pre-eclampsia, prophylaxis with low-dose aspirin and calcium supplements in subsequent pregnancies may be of benefit. Long-term follow-up, particularly in regard to cardiovascular risk, is important in women with a history of hypertensive disorders in pregnancy.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Aspirin can be used to prevent the recurrence of pre-eclampsia in future pregnancies.

4. Gestational hypertension increases the risk of future cardiovascular disease.

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Table 3 **Antihypertensive drugs during breastfeeding**

CLASS	DRUGS CONSIDERED SAFE	AVOID – POTENTIALLY HARMFUL, NO OR LIMITED DATA
Beta blockers	Propranolol, metoprolol, labetalol	Avoid atenolol, no data for other beta blockers
Calcium channel antagonists	Nifedipine	More limited data for diltiazem and verapamil – may be safe; avoid other calcium channel blockers
ACE inhibitors	Captopril, enalapril	Other ACE inhibitors
Angiotensin receptor blockers	None	No data
Thiazide diuretics	None	Limited data
Other	Methyldopa, hydralazine	Limited data for prazosin, consider alternatives

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FURTHER READING

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ARTICLE

Cardiovascular risk factors in Australian children: hypertension and lipid abnormalities

SUMMARY

In children, cardiovascular risk factors are often overlooked but play an important role in later adult cardiovascular health. Lifestyle management and tackling childhood obesity are important, however some children will develop hypertension and dyslipidaemia which requires treatment.

Non-drug treatment should be tried first. Antihypertensive drugs should be reserved for those with secondary hypertension, end-organ damage and those who have not responded to lifestyle measures.

Drug treatment of raised concentrations of low-density lipoprotein cholesterol should be reserved for older children with familial hypercholesterolaemia, very high cholesterol, or those with multiple risk factors for premature coronary artery disease, who do not respond to dietary change.

Introduction

Autopsy studies have found that atherosclerosis occurs in children. Its extent is associated with many of the traditional risk factors for coronary artery disease – lipid abnormalities, hypertension, exposure to cigarette smoke and obesity.[1,2] Several studies have shown, in otherwise healthy children, an association between these risk factors and reduced endothelial function or increased arterial stiffness and wall thickness.[3]

Children with inherited dyslipidaemia, type 1 diabetes and chronic renal dysfunction have impaired vascular function, arterial wall thickening and an increased risk of premature coronary artery disease. Overweight and obese children may have lipid abnormalities, hypertension and insulin resistance. As obesity tends to continue through childhood, these risk factors may be present throughout life. Although it is unclear if obesity in childhood increases the risk of adult coronary artery disease, independent of adult obesity, there is considerable evidence of an adverse effect of obesity on the vascular structure and function of children.

These studies have led to recommendations for the management of cardiovascular risk factors in children who are at increased risk of premature coronary artery disease and in those who are overweight or obese. Although the management is based on lifestyle modification, drugs are increasingly being used for dyslipidaemia and high blood pressure in children.

Screening

Although excellent guidelines exist for cardiovascular risk management in adult Australians[4] there is no equivalent Australian document for children. There are population differences in Australian children which make it prudent to offer some local modifications to the screening and treatment guidelines produced in North America.

High blood pressure

The National High Blood Pressure Working Group in the USA has made recommendations regarding hypertension in children. It suggests opportunistic screening of blood pressure in **all** children older than three years. Children younger than three years should be screened if they have additional risk factors for hypertension such as prematurity or very low birth weight, congenital heart disease, recurrent urinary tract infection or renal disease or are being treated with drugs known to raise blood pressure.[5]

It has yet to be shown that a program of regular childhood screening of blood pressure reduces the risk of adult hypertension or cardiovascular disease. However, measuring blood pressure should be part of the routine physical examination. As high blood pressure in childhood is strongly associated with high body mass, a case can be made for regularly assessing blood pressure in overweight and obese children and in those with a high risk for premature coronary artery disease (Box 1).

Blood pressure should be measured in the right arm, after five minutes of quiet rest, using an appropriately sized cuff (cuff bladder width ≥40% and length 80–100% of the mid-arm circumference). The blood pressure should be considered within the percentiles based on gender, age and height (calculated from www.cdc.gov/growthcharts), with reference to US

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Key words
antihypertensives, antilipidaemic drugs, cholesterol

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Box 1 Suggested groups for regular surveillance of blood pressure in childhood

All adolescents (>12 years)

All children irrespective of age with:

- body mass index >85th percentile
- increased risk of hypertension
- increased risk of premature coronary artery disease – inherited dyslipidaemia, diabetes, chronic kidney disease
- 'repaired' congenital or acquired heart disease

normative data (available at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf).

Dyslipidaemia

The National Cholesterol Education Program produced guidelines for the screening of dyslipidaemia and acceptable levels for cholesterol in American children in 1992.[6] It recommended cholesterol testing in children with a family history of premature coronary artery disease or high cholesterol (Table 1). Recent guidelines from the American Academy of Pediatrics have widened the indications for, and lowered the age of, cholesterol testing.[7] They recommend a fasting lipid profile for children 2–10 years old, with retesting after 3–5 years if the results are normal. The recommendations are to screen:

- all children with a positive family history of dyslipidaemia or premature coronary artery disease
- any child whose family history is unknown
- all overweight and obese children
- all children with other cardiovascular risk factors such as hypertension, cigarette smoking or diabetes mellitus.

One potential rationale for early childhood lipid testing is that lipoprotein levels tend to track from childhood into adult life.[8-10] Serial correlations of lipids over time vary significantly between different studies and also depend upon the type of lipid followed. For total and low density lipoprotein (LDL) cholesterol, approximately 40–55% of children with high concentrations will go on to have elevated levels as young adults. Detection of lipid abnormalities in young children could prompt the changes in lifestyle that will be required throughout life. However, both universal and targeted lipid testing in children still result in a high false-positive rate for adult dyslipidaemia.

In contrast, screening based only on the child's family history may suffer from inaccurate or incomplete information and relies on adult family members having their cholesterol measured. However, more rigorous assessment of family history combined with cholesterol testing in adults, to detect those with significant elevations of LDL, should improve the identification of children at highest risk of future coronary artery disease, namely those with inherited dyslipidaemias such as familial hypercholesterolaemia.

Overweight and obese children commonly have lipid abnormalities, particularly reduced concentrations of high density lipoprotein (HDL) cholesterol and high triglycerides.[11] However, screening of overweight and obese children does not improve the specificity for elevated adult LDL.[9] Although the majority of overweight and obese children with low concentrations of HDL become adults with low concentrations, testing these children will not detect most of the people who have reduced concentrations of HDL in adulthood.

For overweight and obese children, with or without high triglycerides and reduced HDL, the approach to treatment is weight management via changes in diet and physical activity. It is uncertain, particularly in the case of young children, that knowing their lipid profile will lead to a greater motivation to implement such changes. In the majority of overweight and obese children, lifestyle changes may be undertaken without testing their lipids.

In Australia, we suggest that screening for cholesterol abnormalities be reserved for older children (>10–12 years) with a positive family history of dyslipidaemia or premature coronary artery disease, or with other cardiovascular risk factors including overweight or obesity.

Management

Whenever possible management should begin with non-drug treatment.

Hypertension

When hypertension is confirmed in a child (repeated valid blood pressure measurements >95th percentile) the clinical history and examination should consider

Table 1 Classification of cholesterol levels in children and adolescents from families with hypercholesterolaemia or premature cardiovascular disease [6]

CATEGORY	TOTAL CHOLESTEROL (mmol/L)	LDL CHOLESTEROL (mmol/L)
Acceptable	<4.4	<2.8
Borderline	4.4–5.1	2.8–3.3
High	≥5.2	≥3.4

possible secondary causes (see Box 2). Specialist referral is indicated for further evaluation and management.

Non-drug treatment

A large number of studies have shown that diet and physical activity are safe and effective in reducing blood pressure in children.[5] This approach is appropriate for all children with hypertension associated with being overweight or obese. Lifestyle modifications within the whole family are central to the non-drug treatment of hypertension. Although it is difficult to achieve, weight loss is associated with substantial reductions in blood pressure (up to 8–12 mmHg). Mild salt restriction ('no added salt') may produce further small reductions in blood pressure (1–3 mmHg). Referral to a paediatric dietitian is indicated in very young children or in those with severe obesity.

Drug treatment

The long-term cardiovascular benefits of antihypertensive drugs in children are not known and their effects on growth and development are also unknown. However, many classes of antihypertensive drugs have been shown to be safe and effective in lowering blood pressure in children. The indications for antihypertensive treatment in children with blood pressure above the 95th percentile include:

- severe symptomatic hypertension
- secondary hypertension
- presence of other risk factors for premature coronary artery disease (diabetes mellitus, chronic renal disease, inherited dyslipidaemia)
- persistent hypertension despite an adequate trial of non-drug therapy **plus** evidence of end-organ damage.

Factors such as dosing frequency, formulation (availability of a suspension for young children) and the presence of comorbid conditions will have an important impact on the choice of drug. Children should be started on the lowest recommended dose and the dose gradually increased until the desired blood pressure is attained (<95th percentile or <90th percentile in the presence of end-organ damage). A second class of drug may be added if the highest maximal dose is reached or if adverse effects develop on higher doses of the first drug. Of the commonly used antihypertensive drugs, ACE inhibitors and calcium channel blockers are contraindicated in pregnancy; they should therefore be used with caution in females of reproductive age. Contraception should be discussed before prescribing.

Dyslipidaemia

The long-term effects of treating childhood dyslipidaemia are uncertain.

Non-drug treatment

Lifestyle modifications within a whole family are central to the non-drug treatment of dyslipidaemia and hypertension

Diet and increased physical activity are important components of the management of lipid abnormalities in children. They are recommended in all children with borderline or high concentrations of total or LDL cholesterol and in the obese with low concentrations of HDL cholesterol and high triglycerides. Lifestyle modifications within a whole family are central to the non-drug treatment of dyslipidaemia.

Diets with reduced saturated fat and cholesterol may lower total cholesterol by between 5 and 10%. Increasing the intake of soluble fibre and the use of plant sterol or stanol margarines may produce further modest reductions (5–10%) in LDL concentrations. Although short-term data indicate that plant sterols and stanols are safe, long-term studies on their safety in children are required, in relation to decreased absorption of beta carotene and fat-soluble vitamins.

We are unaware of any randomised controlled trials of fish oil supplementation in paediatric dyslipidaemia.

Box 2 **Further evaluation of children with hypertension**

Exclusion of white-coat hypertension

24-hour ambulatory blood pressure monitoring when white-coat hypertension is suspected or when there has been a poor response to therapy

Evaluation for secondary causes

Indications

- <8 years
- extreme blood pressure elevation (>99th percentile + 5 mmHg)
- signs or symptoms of a secondary cause
- failure to respond to therapy

Tests (as determined by detailed history and examination)

- urine – urinalysis, catecholamines, steroids, protein
- blood – chemistry, renin, catecholamines
- renal ultrasound
- renovascular imaging
- echocardiogram – aortic coarctation

Evaluation for end-organ damage

- echocardiogram – left ventricular hypertrophy
- retinal examination

Drug treatment

The guidelines of the American Academy of Pediatrics suggest considering drug treatment in children eight years or older with LDL concentrations of 4.9 mmol/L or more, or 4.1 mmol/L or more in the presence of at least two other risk factors for coronary artery disease. Treatment should also be considered if there is a family history of premature coronary artery disease or an LDL concentration of 3.3 mmol/L or more in the presence of diabetes.[7] Younger children with homozygous familial hypercholesterolaemia and dramatic elevations in LDL concentrations (>12 mmol/L) will also require drug treatment. A proportion of children with homozygous familial hypercholesterolaemia will require plasmapharesis to lower LDL cholesterol.

HMG CoA reductase inhibitors (statins) are currently the first-line drugs for elevated cholesterol in children. In randomised controlled trials in children, statins have resulted in reductions in total (15–30%) and LDL cholesterol (20–40%). Small improvements have also been observed in HDL cholesterol (3–10%). These trials have demonstrated the short-term safety of statins in children, with rare cases of elevations in liver transaminases and creatine kinase. In general, the lower end of the dose range for adults results in substantial reductions in cholesterol in children, with a relatively smaller incremental benefit from higher doses. Children should be monitored for muscle cramping and periodically have blood collected for liver enzymes and creatine kinase.

Bile acid binding resins and niacin may produce effective cholesterol lowering but current preparations are limited by their adverse effect profile. Ezetimibe, a cholesterol-absorption inhibitor, may reduce LDL concentrations by 20% and it is commonly used in adults in combination with statins. Its use in children requires further investigation.

Familial hypercholesterolaemia

Lifestyle modification alone is unlikely to lower LDL sufficiently in patients with heterozygous familial hypercholesterolaemia. However, the specific age to start drug treatment is uncertain. Arterial wall thickness in children with heterozygous familial hypercholesterolaemia begins to diverge from unaffected siblings at around 12 years. A number of randomised clinical trials have shown the short-term safety and efficacy of statins (cholesterol lowering of 20–50%) in these children, even when started between eight and ten years.[12,13] However, evidence for their long-term safety is lacking. Our practice is to exercise caution and reserve statin therapy for older children (>12 years).[14] It may be appropriate to delay statin therapy for longer in girls, until an age when discussions about reproduction and contraception can occur, as statins are contraindicated in pregnancy. A strong family history of premature coronary artery disease, unusually high cholesterol (>9 mmol/L after conservative measures) or a rapid progression in surrogate measures of atherosclerosis (for example ultrasound measurement of carotid arterial wall thickness) may lower the age threshold for therapy.

Conclusion

Cardiovascular risk factors are increasing in children, particularly those who are overweight or obese, which may have an adverse effect on long-term cardiovascular health. The mainstay of management is diet and increased physical activity. Drug treatment of high blood pressure should be reserved for children with secondary hypertension or those with end-organ damage who do not respond to lifestyle measures. Statin treatment of high concentrations of LDL cholesterol should be reserved for older children with familial hypercholesterolaemia, very high cholesterol, or those with multiple risk factors for premature coronary artery disease, who do not respond to dietary change. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. Most obese children have high concentrations of high density lipoprotein.

6. Unlike adults, weight loss does not reduce blood pressure in children.

Answers on page 71

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ARTICLE

Safe use of adrenaline autoinjectors

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allergy, anaphylaxis

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SUMMARY

Adrenaline is the first-line treatment for anaphylaxis. Adrenaline autoinjectors enable non-medical people including patients to treat anaphylaxis.

When a patient is known or suspected to be experiencing anaphylaxis, adrenaline should be given as soon as possible. Delayed administration of adrenaline increases the risk of death.

Patients with anaphylaxis may require further doses of adrenaline. It is therefore important to monitor them in a medical facility for at least four hours after the last dose of adrenaline.

Patients and carers need to be instructed how to use the device they have been prescribed as there are two different brands of autoinjectors available in Australia. They should have an ASCIA Action Plan for Anaphylaxis which is appropriate for their device.

Introduction

Adrenaline autoinjectors are automatic injectors designed to give a single fixed dose of adrenaline. They can be used by non-medical people to treat anaphylaxis. There are two brands of adrenaline autoinjectors available in Australia – EpiPen and Anapen. While there are some similarities, differences exist between the devices (Table 1). EpiPen was redesigned in 2011.

Fig. 1 **Examples of adrenaline autoinjector administration**

EpiPen

Anapen

Both devices can be injected through a single layer of clothing (not through seams or pockets)

How are adrenaline autoinjectors used?

EpiPen and Anapen have different methods of administration. Trainer devices should be used to educate patients on how to use the adrenaline autoinjector prescribed. Adrenaline autoinjectors are not brand substitutable, therefore the device prescribed is what should be dispensed. This is particularly important given the different methods of administration.

EpiPen is designed to be held in the mid-section with the fingers and thumb forming a fist around the device (Fig. 1). The device is activated by removing the safety release and pressing firmly against the outer mid-thigh until a click is heard. Colour-coded ends have been used in its design to facilitate correct administration. The orange needle sheath of the new look EpiPen extends after use to prevent needle-stick injury after the device has been activated.

The administration of Anapen requires the removal of the black needle shield and grey safety cap. Anapen is held firmly against the outer mid-thigh and is activated by depressing a red button with the thumb, so it clicks (Fig. 1).

Both devices should be held in place for 10 seconds after activation. The injection site should be massaged after the device is withdrawn.

Prescribing guidelines

Adrenaline autoinjectors are recommended for people at risk of anaphylaxis (Table 2). As EpiPen and Anapen are Schedule 3, they are available without prescription at full price. They are also available on the Pharmaceutical Benefits Scheme (PBS) by authority prescription when the risk and clinical need have been assessed by, or in consultation with, a clinical immunologist, allergist, paediatrician or respiratory physician. They can also be prescribed on discharge from hospital or an emergency department after patients have been treated with adrenaline for anaphylaxis. Adults and children are able to obtain two adrenaline autoinjectors (same brand) on PBS authority prescription. If there is a delay in access to an immunology or allergy specialist, general practitioners can contact the specialist for approval to prescribe the initial adrenaline autoinjector. The patient must be referred to a specialist for diagnosis, education and assessment for immunotherapy (for example for bee sting anaphylaxis). Once a patient has been prescribed an adrenaline autoinjector by authority prescription, subsequent prescriptions can be provided by general practitioners.

Dose guidelines

There are three available doses of adrenaline autoinjectors. The doses relating to bodyweight given in the product information are different from the recommendations of the Australasian Society of Clinical Immunology and Allergy (ASCIA). The following ASCIA recommendations are based on consensus and standard practice by ASCIA members:

- for children under 10 kg (under one year) adrenaline autoinjectors are not usually recommended. (In some circumstances a 0.15 mg adrenaline autoinjector device may be prescribed)
- for children 10–20 kg, 0.15 mg adrenaline autoinjector device
- for children over 20 kg and adults, 0.3 mg adrenaline autoinjector device.[1]

Anapen 0.5 mg will be available in Australia in 2012. Consideration may be given to prescribing Anapen 0.5 mg for any patient over 60 kg. Assessment of the need for a 0.5 mg dose should be undertaken by the prescribing physician, taking into account risk factors for anaphylaxis and the presence of comorbidities. For detailed information see the ASCIA Guidelines for Adrenaline Autoinjector Prescription on the ASCIA website (www.allergy.org.au).

Table 1 **Adrenaline autoinjector feature comparison**

FEATURE	EPIPEN	ANAPEN
Adrenaline dose	Single pre-measured	Single pre-measured
Colour of 0.15 mg device label	Green	Green
Colour of 0.3 mg dose device label	Yellow	Yellow
Colour of 0.5 mg dose device label	Not available	Magenta
Viewing window to check adrenaline for discolouration or precipitate	Yes	No
Availability	S3 (over-the-counter at full price) 2 devices on Pharmaceutical Benefits Scheme authority prescription	S3 (over-the-counter at full price) 2 devices on Pharmaceutical Benefits Scheme authority prescription*
Activation of device	Press firmly against outer mid-thigh	Depress red button when device on outer mid-thigh
Safety	Blue safety release Orange needle end automatically extends over needle after use	Grey safety cap Black needle shield can be replaced over needle after use
Trainer devices	Available from distributor of device	Available from distributor of device
Expiry reminder service	EpiClub	Analert

* At the time of writing this article, an application for PBS authority prescription for 0.5 mg Anapen had been submitted

Table 2 **Guidelines for prescribing adrenaline autoinjectors** *

PATIENT HISTORY	RECOMMENDATIONS
History of anaphylaxis	Always recommended
History of generalised allergic reaction, other than anaphylaxis, with one or more of the following risk factors: Age (children over 5 years, adolescents and young adults) Specific allergic triggers: • tree nut/peanut allergy • stinging insect allergy in adults (bees, wasps, jumper ants) Comorbidity: asthma (concurrent or past history), history of arrhythmia Limited access to emergency medical care	Sometimes recommended
Asthma with no history of anaphylaxis or generalised allergic reactions	Not normally recommended
Elevated specific IgE only (positive serum allergen specific IgE test (formerly known as RAST) and/or skin test) without a history of clinical reactions	
Family (rather than personal) history of anaphylaxis or allergy	
Resolved food allergy	
Generalised skin rash (only) to bee stings – in children	
Local reactions to insect stings – in adults and children	

* Abbreviated from Australasian Society of Clinical Immunology and Allergy guidelines for adrenaline autoinjector prescription [1]

What needs monitoring?

As with adrenaline ampoules, the expiry date on the adrenaline autoinjectors needs to be checked regularly. By the time of dispensing the shelf life is usually less than two years. Adrenaline is heat sensitive and should be stored at room temperature. Adrenaline autoinjectors should never be refrigerated as this can affect the autoinjector mechanism. EpiPen has a viewing window enabling patients to check if the adrenaline is discoloured or contains a precipitate, which may reduce the effectiveness of the adrenaline.

Common adverse effects and important precautions

After an adrenaline injection, transient and minor adverse effects occur in most patients. They include anxiety, fear, restlessness, headache, dizziness, palpitations, tremor and pallor. Studies have shown minimal cardiovascular effects in children.[2] Serious adverse effects are rare.

Intramuscular adrenaline (1:1000) in doses of 0.01 mg/kg is not associated with clinically significant cardiotoxicity, even if given inadvertently in the absence of acute anaphylaxis.[3] The reluctance to give adrenaline due to fear of adverse cardiac effects should be countered by the awareness that coronary artery spasm, myocardial ischaemia and infarction, and dysrhythmias can occur in untreated anaphylaxis.[4,5] However, patients on non-selective beta-blocking drugs may experience severe hypertension[6] and bradycardia when they are given adrenaline.

Precautions are relative as adrenaline autoinjectors are intended for use in life-threatening anaphylaxis. There are no absolute contraindications to the administration of adrenaline for anaphylaxis.[7]

Patients should be monitored by a health professional for a minimum of four hours after the last dose of adrenaline. This is in case further doses are needed.

ASCIA Action Plans

ASCIA Action Plans and anaphylaxis e-training for health professionals are available from the website www.allergy.org.au. These action plans include the signs and symptoms of anaphylaxis and provide instruction on when and how to use an adrenaline autoinjector. All patients who are prescribed an adrenaline autoinjector should be given a personal ASCIA Action Plan for Anaphylaxis completed by their medical practitioner. Patients should be educated to **always** carry their adrenaline autoinjector and ASCIA Action Plan.

There are three types of ASCIA Action Plans:

- ASCIA Action Plan for Allergic Reactions (green) is provided to patients with mild or moderate allergic reactions who are not considered at risk of anaphylaxis and who have not been prescribed an adrenaline autoinjector
- personal ASCIA Action Plan for Anaphylaxis (red) is provided to patients at risk of anaphylaxis to any allergen who have been prescribed an adrenaline autoinjector
- general ASCIA Action Plan for Anaphylaxis (orange) is useful as a poster or for storage with an adrenaline autoinjector in first aid kits.

Conclusion

Anaphylaxis is potentially life threatening and must be treated as a medical emergency. Adrenaline autoinjectors enable prompt administration of adrenaline in an anaphylaxis emergency. Patients must be dispensed the adrenaline autoinjector prescribed, and be shown how to administer it using a trainer device. They should also be advised to always carry their device and ASCIA Action Plan. ASCIA Action Plans for Anaphylaxis provide instructions on when and how to give the adrenaline autoinjector.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Adrenaline should not be used to treat anaphylaxis in patients taking beta blockers.

8. Patients with high concentrations of IgE, but no history of anaphylaxis, should carry an adrenaline autoinjector.

Answers on page 71

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ARTICLE

Transcranial magnetic stimulation-based methods in the treatment of depression

SUMMARY

A substantial proportion of patients fail to respond to standard treatments for depression. Several new methods of stimulating the brain are being developed as alternative interventions for these and other patient groups.

Repetitive transcranial magnetic stimulation is a method of brain stimulation that involves the application of repeated magnetic pulses to directly activate cortical neurones. Several studies show it has antidepressant efficacy.

There are few adverse effects of repetitive transcranial magnetic stimulation. However, the optimal stimulation parameters are not yet fully established.

Introduction

Major depressive disorder is common and disabling with a lifetime prevalence of around 15%.[1] There are a range of psychosocial treatments and drugs for depression. Despite these options, approximately 30% of patients remain unwell with 'treatment-resistant depression' resulting in substantial suffering as well as high treatment costs.[2] The main established treatment option for patients with treatment-resistant depression is electroconvulsive therapy (ECT) but this has cognitive adverse effects, requires general anaesthesia and has a stigma associated with it.[3] This has prompted research into new methods of brain stimulation.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) has recently been developed as an additional option for treatment-resistant depression. It may also have a role for patients who cannot tolerate other treatments.

rTMS involves the application of a rapidly time variable magnetic field, administered via a coil placed over the scalp, to stimulate brain activity[4] (see Fig. 1). A high voltage current in the coil generates a focused magnetic field which passes into the brain and induces an electrical field. This induces depolarisation of superficial cortical neurones.[4] Repeated high frequency stimulation increases brain activity, and low frequency stimulation decreases it.[5] rTMS can be applied either directly to nonconvulsively modulate brain activity or to induce a focused seizure (magnetic seizure therapy).

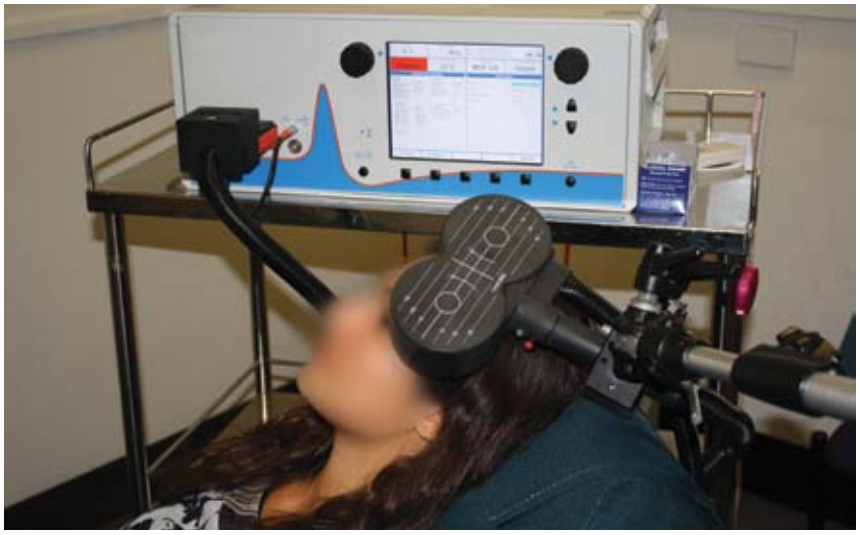
Procedure

rTMS is usually given in a discrete course, most commonly daily for between 15 and 30 consecutive weekdays. Treatment sessions, which can safely be provided to outpatients, take between 30 and 45 minutes and there are no restrictions on what patients are able to do after the treatment. rTMS needs a medical prescription and administration by an appropriately trained healthcare professional who can deal with a seizure if one occurs.[6] No sedation or anaesthetic is required.

Efficacy in depression

Standard nonconvulsive rTMS has been investigated as a treatment for depression since the mid-1990s. The standard strategy applies repeated high frequency pulses to the left dorsolateral prefrontal cortex. This region of the brain appears to be underactive in the brain scans of depressed patients.[7,8] There have been more than 30 double-blind placebo-controlled trials of this method and several meta-analyses. One meta-analysis of 30 trials and 1164 patients found a highly significant effect ($p<0.00001$) of active treatment compared to sham treatment on the

Fig. 1 **Repetitive transcranial magnetic stimulation procedure**



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brain stimulation, electroconvulsive therapy, magnetic seizure therapy

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average reduction in depression severity scores.[9] The effect sizes seen with rTMS are similar to those seen with antidepressant drugs,[10] despite many of the trials enrolling patients with treatment-resistant depression. However, it is notable that response rates across the trials are usually less than 50%, and remission rates are often much lower. Very modest response rates were seen in the two large multisite trials conducted to date, one sponsored by a device manufacturer[10] and one independently funded by the US National Institute of Mental Health.[11] Both found statistically significant benefits of rTMS over sham treatment. The first of these trials[10] was used to support a successful application to the US Food and Drug Administration which approved the treatment in 2008.

Comparison with ECT (Table 1)

The trials which have compared rTMS to ECT[12-15] have generally been underpowered to identify between-treatment differences. Their design is often biased towards a likely finding of a benefit of ECT as longer and more flexible courses of ECT, for example including both unilateral and bilateral approaches, were generally provided. Two studies have shown an advantage of ECT, and an advantage of ECT was supported in a recent meta-analysis of six studies.[16] However, none of these rTMS studies included treatment beyond 20 sessions and all used treatment intensities (percentage of maximum machine output) and total numbers of rTMS pulses below what is now generally considered optimal. ECT clearly produces a faster treatment response than rTMS, although accelerated rTMS protocols are showing some promise in rapid symptom improvement.[17]

Adverse effects

One of the major benefits of rTMS is its benign adverse effect profile.[18] Some patients find the treatment uncomfortable or experience a transient headache afterwards, but there are no other major reported adverse effects. rTMS can induce seizures but the risk is extremely low when treatment is applied following standard safety guidelines.[19] The induction of mania is possible in patients with bipolar disorder, but has not been reported in unipolar depression.[20]

Uncertainties

Standard left-sided rTMS clearly has antidepressant properties but there are a range of issues that remain unresolved. These include the optimal method of administration. Other forms of rTMS such as low frequency stimulation applied to the right dorsolateral prefrontal cortex and bilateral rTMS also have efficacy.[21] Other uncertainties include the individualisation of treatment parameters and the evaluation of maintenance protocols to limit the problematic issue of depressive relapse. rTMS also appears a useful treatment for patients with relative contraindications to drugs and ECT or when there is a wish to avoid these treatments, such as during pregnancy, but only limited data on such uses are currently available.[22]

Magnetic seizure therapy

The therapeutic benefits of ECT may be related to the seizure, rather than the direct electrical current. Researchers are investigating the effects of using rTMS to provoke a seizure. This requires rTMS to be applied at a frequency and intensity beyond that used in standard therapy. As with ECT, a general anaesthetic is required.

Several human trials of magnetic seizure therapy have begun but currently insufficient data are available to confirm its place in treatment. Open-label data and a small comparative trial[23] have suggested that it might have similar efficacy to ECT with fewer cognitive adverse effects, although this conclusion is still very preliminary.

Table 1 **Characteristics of repetitive transcranial magnetic stimulation and electroconvulsive therapy**

	REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION	ELECTROCONVULSIVE THERAPY
Action	Nonconvulsive	Convulsive
Indications	Treatment-resistant depression	Severe depression
	Failure to tolerate other treatments for depression	Treatment-resistant depression
	Possible first-line treatment based on patient choice	Catatonia
		Emergency treatment of depression requiring urgent clinical response
Efficacy	Moderately well established	Well established
	Response rates <50%	Response rates >50%
Safety	Low risk of seizure induction	Risks associated with general anaesthesia
	No cognitive adverse effects	Memory impairment, possible other cognitive adverse effects
	No general anaesthetic	

Conclusion

A range of novel brain stimulation technologies are currently under active investigation for the treatment of depression. rTMS has progressed down this developmental path to a point where it is currently entering into clinical practice. However, further research is still required to optimise its application. Its availability in Australia is currently limited by the lack of a Medicare rebate for treatment. Only limited treatment programs subsidised by hospital services and without direct patient charge are currently accessible in some private and public hospitals. Magnetic seizure therapy is at an earlier stage of development but there are some promising preliminary results.

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SELF-TEST QUESTIONS

True or false?

9. Unlike electroconvulsive therapy, repetitive transcranial magnetic stimulation therapy does not require a general anaesthetic.

10. Repetitive transcranial magnetic stimulation therapy induces remission in more than 50% of patients with treatment-resistant depression.

Answers on page 71

DIAGNOSTIC TESTS

Home sleep studies

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Key words
CPAP, polysomnogram, sleep apnoea, sleep laboratories

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SUMMARY

Home sleep studies have evolved beyond home oximetry to a polysomnogram only marginally different from that found in a sleep laboratory.

They are now a well accepted way of investigating sleep apnoea and comprise up to 30% of all Medicare-funded sleep studies in Australia.

For a home sleep study to be effective, a number of important elements must be in place, including the input of the referring doctor, the correct use of the equipment by the patient, a skilful technician and accurate scoring of the raw data.

Interpretation of a sleep study by a sleep physician with the clinical and demographic information and recommendation of appropriate management is also essential.

Although home sleep studies allow more patients to be assessed and treated, particularly those in country areas, if any element is deficient the outcome may be suboptimal.

Introduction

The use of continuous positive airway pressure (CPAP) in obstructive sleep apnoea has spawned a multimillion dollar industry worldwide for the treatment of sleep disordered breathing.[1] The real prevalence of obstructive sleep apnoea in the community is difficult to ascertain as it varies with age, gender, body mass index, menopausal status and family history. How one defines 'abnormal' can also vary.[2,3]

There is a large overlap in the symptoms of depression and sleep apnoea, which often coexist and may be intertwined in their aetiology. It is not uncommon to see sleep apnoea go undiagnosed for years in patients with depression. There are many other related comorbidities including obesity, hypertension, ischaemic heart disease, cerebrovascular disease, diabetes, dyslipidaemia, fatty liver and sexual dysfunction.

The social and financial cost of sleep apnoea is substantial, with numerous secondary effects such as motor vehicle and work accidents. Treating sleep apnoea is very cost-effective in the long term not only for the individual but for the whole community.[4]

Patient selection for sleep investigations

The primary aim of home studies is to diagnose sleep-disordered breathing. If other conditions are considered likely, the patient should be referred to a sleep physician first.

There are numerous indications for a home sleep study. However to avoid their overuse, a global assessment of the patient should be done first. The common symptoms and clinical features, alone or in combination, which should invoke concern include:

- unrefreshing and restless sleep, particularly in a snorer
- nocturnal startles and choking episodes
- nocturia
- witnessed apnoeas
- night sweats, insomnia and restless sleep
- cognitive impairment
- sexual dysfunction
- depression
- sleep-related driving 'incidents'
- systemic or pulmonary hypertension
- nocturnal arrythmias and angina.

A high clinical suspicion for sleep apnoea is recommended in patients with potentially dangerous occupations.

Measuring sleep disorders

The past 20 years have seen a steady increase in private and public sleep laboratories in Australia. They are costly to run with ever-changing computers and software as well as high labour costs. A ratio of one overnight sleep technician to three patients is common. Many patients still depend on public hospital sleep laboratories with their long waiting lists and limited resources.

There were 6400 sleep laboratory polysomnograms per month from January 2009 to February 2011, based on Australian Medicare data. Of these, the proportion of Medicare-funded home polysomnograms has increased from around 20% in early 2009 to 32% by December 2010.

A Canadian study comparing a sleep laboratory polysomnogram with an autotitrating CPAP pump

with no polysomnogram, found no overall difference in outcome in high-risk patients.[5] An Australian study also showed no overall difference in outcome in those having a CPAP autotitration at home rather than one in a sleep laboratory.[6] However, these findings need to be weighed against the potential for inappropriate use of home polysomnograms for marginal indications.

Home oximetry

The portable oximeter is a fairly sensitive test for sleep apnoea when the apnoea causes moderate to severe hypoxaemia. However, it is less sensitive for detecting mild to moderate cases of nocturnal hypoxaemia, which may still be very symptomatic because of sleep disruption from frequent respiratory arousals. As many symptomatic patients have little if any oxygen desaturation, nocturnal oximetry is a fairly insensitive tool for a significant proportion of sleep apnoea sufferers, as excessive daytime somnolence is more due to respiratory arousals than hypoxic events.

Sleep studies at home

Many patients prefer a sleep study in their own bed – it is more convenient and cheaper. It is now possible to produce data from a home sleep study that are equal to a sleep laboratory polysomnogram.

Portable polysomnogram monitors are about the size of a small transistor radio. They monitor nasal airflow, electroencephalogram, electrocardiogram, electromyography, oximetry and chest, abdominal and leg movements. These devices have been well validated in numerous studies with the gold standard of the sleep laboratory polysomnogram.[7] The main difference between the home study and the sleep laboratory polysomnogram is not the data, but the technician in attendance all night to adjust electrodes, ensure data quality and observe the activities of the patient both asleep and awake.

One negative feature of inpatient studies is that some patients do not sleep as well in a sleep laboratory as they would at home. However, with home studies, if electrodes fall off the patient may be oblivious of this until morning and some home sleep studies do not monitor leg movements. In addition, they also may miss less common sleep disorders, such as nocturnal seizures or parasomnia.

The essential elements

For a successful home sleep study, from my experience many elements are required. If any element is deficient, the outcome may be suboptimal.

General practitioner

The general practitioner needs a working knowledge of sleep apnoea to ensure that referrals are appropriate. Inappropriate referrals often present difficulties in interpretation and recommendations for the reporting sleep physician. The general practitioner should consider the practicalities of eventual treatment options before the sleep study is done. For example, a frail elderly patient is unlikely to cope with a CPAP mask and pump.

It is essential to select patients who are able to apply the sleep equipment and keep it on during the night. A home sleep study on an elderly patient with cognitive impairment or severe Parkinson's disease is usually doomed to failure. Correct patient selection for the home studies, or for that matter an inpatient study, is an essential element which may ultimately dictate the success or failure of the test. For most home studies, patients who are 'computer savvy' are more capable of managing electrodes and oximeters.

Equipment

This is the least problematic of the elements as it is robust. Electrodes and an oximeter are relatively easy to apply and remove. The commonest problems encountered are an oximeter trace dropping off during the night or from improperly applied electrodes. The equipment usually comes with photographs showing how to place the electrodes and oximeter.

Technician

The technician needs a good working knowledge of not only sleep apnoea, but also other common sleep pathologies and comorbidities. The technician should take a history, record medications, measure body mass index and provide demographic data which are essential for the reporting physician.

Data analysis

After the study, the technician uploads the data to a remote centre where it is collated and scored by sleep scientists. It is then sent to the sleep physician with the raw data and the patient's history, symptoms, medications and demographics.

Sleep physician

The sleep physician reports the results of the sleep study and recommends treatment. They ascertain whether the sleep scoring is reliable and consider the results in light of the clinical indications and other patient factors such as comorbidities and occupation, such as school bus driver. Knowing the patient's medications is also important and may explain, for example, the lack of REM (rapid eye movement) sleep, why a person is excessively sleepy or is having a lot of central sleep apnoea (for example from opioids). Reporting is hindered by inadequate clinical details.

Although I recommend that patients having difficulties with CPAP should see a sleep physician, only a small proportion of them do. Sleep physicians often fine-tune treatment of sleep apnoea in more difficult cases including complex sleep apnoea. Their global assessment adds significant value to the general management of these patients, particularly in finding the cause and diagnosing and managing other comorbidities. The sleep physician's broad training, not only in sleep disorders but in general medicine and the psychiatric aspects of sleep, provides an important oversight. All patients with sleep apnoea adversely affecting their driving or with a potentially dangerous occupation should be seen by a sleep physician. To do otherwise could have legal ramifications.

Other requirements

Other secondary elements are also needed, for example dietitians and dentists for mandibular splints. Patients may also need a support person to assist them with treatment.

Conclusion

Home sleep studies are a viable alternative to laboratory sleep studies and are here to stay. I predict they will eventually be the main screening tool for sleep apnoea in the community complementing the important role of the sleep laboratory polysomnogram. For home sleep studies to be effective, several elements are required, including a patient who can use the equipment. Patients with more complicated sleep apnoea, multiple comorbidities and serious other sleep disorders should see a sleep physician. ◁

Professor Allen does reporting of home sleep studies for Healthy Sleep Solutions, but has no financial interest in the company.

Q:

SELF-TEST QUESTIONS

True or false?

11. The devices for home sleep studies have not been validated against sleep laboratory polysomnograms.

12. Opioids can cause central sleep apnoea.

Answers on page 71

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Medicinal mishap

Dabigatran – a new safe drug to replace an old poison?

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Case

An 89-year-old woman was admitted to hospital with melaena. She had a history of atrial fibrillation, type 2 diabetes complicated by hypertension, ischaemic heart disease and nephropathy (creatinine clearance of 29 mL/min, using the Cockcroft-Gault equation).

The patient was taking several drugs for her conditions. These included warfarin which she had taken for 12 years, without any adverse events. Three weeks before admission she was switched to dabigatran, 110 mg twice a day, for prevention of stroke in association with atrial fibrillation.

On admission, her serum creatinine was elevated (172 micromol/L with an estimated creatinine clearance of 18 mL/min) and her haemoglobin was 61 g/L. Despite warfarin therapy ceasing three weeks earlier, the INR was 2.5 and the activated partial thromboplastin time (aPTT) was 84 seconds (normal range 25–35 seconds).

There is no specific antidote for dabigatran. She was given fresh frozen plasma, vitamin K and six units of packed red cells.[1] Upper gastrointestinal endoscopy found no pathology and the bleeding settled spontaneously.

The patient required prolonged rehabilitation after the haemorrhage. She was not discharged home until two months later.

Comment

Dabigatran, a direct thrombin inhibitor, is approved in Australia for stroke prevention in patients with non-valvular atrial fibrillation and at least one other risk factor for stroke. Since 2009, the Therapeutic Goods Administration has received 297 reports of adverse drug events associated with dabigatran[2] and the European Medicines Agency recently reported 256 fatal bleeding events worldwide.[3] The US Food and Drug Administration is reviewing postmarketing reports of major bleeds.[4] Other organisations have released formal recommendations for the use of dabigatran.[5]

Compared to warfarin, the risk of major bleeding in a large clinical trial of dabigatran for stroke prevention in atrial fibrillation was equivalent (at 150 mg twice daily) or less (at 110 mg twice daily).[6] Important exclusion criteria in this trial included 'a condition that increased the risk of haemorrhage', active liver disease and a creatinine clearance less than 30 mL/min. A *post hoc* analysis of this trial suggested the risk of bleeding with dabigatran may be greater in patients over 75 years of age.[7]

Currently, no assay of dabigatran's effect on coagulation is available and monitoring is not recommended. Interpretation of the INR is problematic with dabigatran, as results are variable and not predictable. An aPTT more than twice the reference range is suggestive of over-anticoagulation.[8] Of interest, when enoxaparin was first marketed no monitoring was deemed necessary, however, factor Xa monitoring is now increasingly used.[9]

Dabigatran possesses clinically important pharmacokinetic properties.[10,11] It is predominantly renally cleared with a half-life of 12–14 hours in patients with normal renal function. The half-life is extended as renal function declines. Current recommendations suggest withholding therapy when creatinine clearance is less than 30 mL/min. Although not relevant to this case, dabigatran is a P-glycoprotein substrate and therefore has the potential to interact with P-glycoprotein inhibitors such as amiodarone and verapamil.

Conclusion

This case highlights the dangers of switching patients stabilised on treatment to newer therapies, especially if there are few data on safety and effectiveness in a particular group of patients. The risk of a drug in 'real world' use is often underestimated in clinical trials, as they are often designed to demonstrate efficacy rather than test safety. The trials generally study a highly selected patient group – with a long list of exclusions designed to mitigate risk – and the patients are intensively followed in a manner not typically feasible in routine practice. The true risk of a drug is generally unclear until there is considerable postmarketing experience.

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 3, Number 2, April 2012

In this issue

- Change in the pregnancy category for topiramate
- Use of 2012 seasonal influenza vaccines in children
- Dasatinib (Sprycel) and pulmonary arterial hypertension
- Pulmonary oedema associated with topical phenylephrine

Change in the pregnancy category for topiramate

The TGA is advising health professionals of the change in the pregnancy category for topiramate-containing products from B3 to D.

Topiramate is indicated for the treatment of epilepsy in adults and children aged two years and over, and for the prophylaxis of migraine headache in adults. There are also reports of off-label use of topiramate to assist with weight loss.[1]

The Australian Product Information (PI) already contains warnings regarding the potential effects on the fetus, and recommends that women considering using topiramate receive pregnancy counselling to ensure they are aware of the potential risks to the fetus.

In May 2011, the US Food and Drug Administration advised that there were new data from the North American Antiepileptic Drug Pregnancy Registry that showed an increased risk for the development of cleft lip and/or palate in infants exposed to topiramate during the first trimester of pregnancy.

Following a review of these data, the TGA has changed the pregnancy category for topiramate products from Australian Pregnancy Category B3 to Category D.

Category D medicines are defined as 'Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.'

The PI has been updated to reflect this change and to incorporate this new data in the Precautions section.[2] More information about prescribing medicines in pregnancy is available from the TGA website.[3]

Information for health professionals

Health professionals should advise women of childbearing age of the increased risk for oral clefts when topiramate is used during pregnancy.

Topiramate should be used in pregnancy only if the potential benefits outweigh the potential risks to the fetus. Consideration should be given to prescribing other medicines that have a lower risk of adverse birth outcomes in women of childbearing age.

If a decision is made to prescribe topiramate, health professionals should recommend an appropriate method of contraception for women. In doing so, it should be borne in mind that there is the potential for decreased contraceptive efficacy when using topiramate with estrogen-containing contraceptives.[2]

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

TGA Health Safety Regulation

Use of 2012 seasonal influenza vaccines in children

The TGA advises health professionals that for the 2012 influenza season, there are four influenza vaccines registered for use in children from the age of 6 months – Agrippal, Fluarix, Influvac and Vaxigrip. An additional influenza vaccine, Fluvax, is registered for use in children from the age of 5 years. However, health professionals are advised of special precautions which apply to the use of Fluvax in children aged between 5 and 9 years of age.

During the 2010 influenza season an excess number of febrile reactions and febrile convulsions occurred in children under 5 years of age following immunisation with one of the registered seasonal trivalent influenza vaccines, Fluvax.[1] Consequently, in 2011 the TGA recommended that only Influvac and Vaxigrip vaccines be used in children aged between 6 months and 5 years. These vaccines had been used in Australian children in 2010 and had not been shown to be associated with an increased rate of fever or febrile reactions. Two additional vaccines, Agrippal and Fluarix, had not been supplied in Australia in 2010, and the sponsors had been unable to establish active surveillance to monitor the safety of their vaccines in paediatric populations for the 2011 season. Therefore, the TGA recommended against the use of Agrippal and Fluarix in children under the age of 9 years in 2011.

Recommendations for use in 2012

The sponsors of Agrippal and Fluarix have submitted additional data to the TGA to support the safety of their vaccines in children. The data submitted included the experience with their vaccines in the:

- 2011 Southern Hemisphere winter; and
- 2011/2012 Northern Hemisphere winter.

Following evaluation, the TGA has found these data raise no safety concerns related to fever or febrile convulsions in children who received either vaccine. The TGA now considers that Agrippal and Fluarix may be used in children from the age of 6 months, noting there has been no change to the strains in the vaccine to affect the safety profile of the vaccines in 2012.

Those providing immunisations should note that special precautions apply to the use of Fluvax in children between 5 and 9 years of age. Febrile events have been observed in children aged 5 to 9 years following immunisation with Fluvax. Therefore, in this age group, a decision to vaccinate with the 2012 Fluvax vaccine should be based on careful consideration of potential benefits and risks in the individual.

The TGA has registered five vaccines for use in children for the 2012 influenza season, with the indications shown in the following table.

An additional vaccine, Intanza (Sanofi Pasteur), is only registered for use in adults aged 18 to 59 years.

For further information on individual vaccines, please refer to the relevant Product Information document.

Vaccine	Sponsor	Approved indication
Agrippal	Novartis	6 months and over
Fluarix	GSK	6 months and over
Influvac *	Abbott	6 months and over
Vaxigrip *	Sanofi Pasteur	6 months and over
Fluvax †	CSL	5 years and over

* These vaccines also have a paediatric 0.25 mL ('junior') presentation registered for use in children aged 6–35 months

† Febrile events have been observed in children aged 5–9 years following immunisation with Fluvax. Therefore, in this age group a decision to vaccinate with the 2012 Fluvax vaccine should be based on careful consideration of potential benefits and risks in the individual.

Reporting of adverse events following influenza vaccine

Health professionals are encouraged to report all adverse events associated with influenza vaccination in patients of any age to the TGA or through the current requirements in their State or Territory. All reports contribute to the TGA's ongoing monitoring of the safety of influenza vaccines.

REFERENCE

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MEDICINES SAFETY UPDATE

Dasatinib (Sprycel) and pulmonary arterial hypertension

Pulmonary arterial hypertension is known to be a serious but rare adverse event associated with dasatinib therapy. Physicians and general practitioners with patients taking dasatinib are urged to be vigilant for this adverse effect and report any suspected cases of pulmonary arterial hypertension associated with the use of the medicine to the TGA.

Dasatinib (Sprycel) is an oral tyrosine kinase inhibitor approved for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) and Ph+ acute lymphoblastic leukaemia (ALL).

Pulmonary arterial hypertension (PAH) is a rare subtype of pulmonary hypertension, characterised by smooth muscle cell hyperplasia and vascular remodelling of the pulmonary arteries. This results in elevated mean pulmonary arterial pressure (>25 mmHg at rest or >30 mmHg during physical activity) as measured by right heart catheterisation.[1]

Detection and reporting

In the five years from June 2006, 60 serious cases of pulmonary hypertension were reported worldwide in association with dasatinib use to the sponsor's global pharmacovigilance database. Of these 60 cases, 36 cases were reported as pulmonary hypertension, and 24 cases were reported as PAH, including a subset of 12 cases of PAH confirmed by right heart catheterisation. In these 12 cases, PAH was reported after initiation of therapy with dasatinib, including after more than one year of therapy. Patients diagnosed with PAH during dasatinib therapy were often taking concomitant medications and had comorbidities in addition to the underlying malignancy.

To date, the TGA has received one report of reversible PAH secondary to dasatinib treatment for CML.

PAH has an insidious onset and patients with early or mild disease may be asymptomatic. Dyspnoea and reduced exercise capacity are typical early symptoms, which may progress to angina, exertional near-syncope, and signs of right heart failure. Given the high degree of clinical suspicion necessary to make the diagnosis, many cases may be undiagnosed and go unreported.

PAH may be at least partially reversible following cessation of dasatinib. Improvements in haemodynamic and clinical parameters have been observed in patients with PAH following cessation of dasatinib therapy.

The potential for a class-effect involving other tyrosine kinase inhibitors has not yet been investigated. The related drugs, imatinib and nilotinib, have not been implicated in reports of PAH to date. Compared with these, dasatinib appears to have a broader range of activity, affecting multiple kinase and non-kinase targets.[2] This provides a possible explanation for dasatinib-associated PAH and the observed differences in toxicities of drugs within this therapeutic class.

Important information for prescribers

Before commencing dasatinib therapy, patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease. Patients taking dasatinib who develop symptoms of PAH, such as dyspnoea and fatigue, should be evaluated for more common aetiologies, including pleural effusion, pulmonary oedema, anaemia or lung infiltration. Treatment should be withheld in these patients during evaluation. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, dasatinib should be permanently discontinued. Further information is available in the dasatinib Product Information.[3] Prescribers are encouraged to report any suspected cases to the TGA.

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MEDICINES SAFETY UPDATE

Pulmonary oedema associated with topical phenylephrine

Health professionals are reminded of the potential for serious systemic adverse effects, including pulmonary oedema, when topical phenylephrine is used concomitantly with a beta blocker.

Evidence of risk

Phenylephrine, an alpha agonist, is used as a topical vasoconstrictor in ear, nose and throat surgery and as a pupil dilator in eye surgery. There are published case reports of patients who developed pulmonary oedema associated with topical phenylephrine used in the perioperative setting.[1] In the majority of cases, this occurred after a beta blocker was given in an attempt to correct hypertension likely due to systemic absorption of the topical phenylephrine.

Published guidelines

The New York State Department of Health developed guidelines following the intraoperative death of a four-year-old attributed to topical phenylephrine.[1]

These guidelines advise that:

- the lowest effective dose of topical phenylephrine should be given to minimise the potential for systemic adverse effects
- beta blockers and calcium channel blockers should not be used to treat alpha agonist-induced hypertension (as a result of systemic absorption)
- anaesthetists should be consulted prior to administration of phenylephrine (or any other medication) to the surgical site.

REFERENCE

1. Groudine SB, Hollinger I, Jones J, DeBouno BA. New York State Guidelines on the topical use of phenylephrine in the operating room. Anaesthesiology 2000;92:859-64.

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, 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 August 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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New drugs

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

Linagliptin

Approved indication: type 2 diabetes
Trajenta (Boehringer Ingelheim)
5 mg tablets
Australian Medicines Handbook section 10.1.3

Patients with diabetes produce less of the peptide hormones known as incretins. Their concentration can be increased by inhibiting the enzyme (dipeptidyl peptidase 4) which metabolises them. This increases insulin secretion and lowers glucose concentrations. Saxagliptin, sitagliptin, vildagliptin and now linagliptin are all inhibitors of the enzyme (see: Incretin mimetics and enhancers, Aust Prescr 2008;31:102-8).

Linagliptin is taken once a day. Its bioavailability is only 30% and this can be reduced by drugs, such as rifampicin, which induce the P-glycoprotein transporter. The metabolism of the drug involves cytochrome P450 3A4, but this may not be clinically important. Most of the dose is excreted unchanged in the faeces. The terminal half-life of the drug exceeds 100 hours.

Several thousand patients have been involved in trials of linagliptin. These studies included combinations with other treatments for type 2 diabetes as well as monotherapy. In 503 patients with inadequately controlled diabetes, 24 weeks of monotherapy had a significantly greater effect than placebo. From a baseline mean of 8%, the mean glycated haemoglobin (HbA1c) reduced by 0.44% with linagliptin 5 mg, but increased by 0.25% with placebo.[1] In Australia however, linagliptin is only approved in combination with metformin, a sulfonylurea or both.

Another 24-week trial randomised 701 patients whose diabetes was not controlled by metformin. A group of 523 patients took linagliptin and 177 took placebo. From a baseline of 8.09%, the HbA1c reduced by 0.49% with linagliptin 5 mg and increased by 0.15%, from 8.02%, with placebo. A target HbA1c of 7% or less was achieved by 26% of the linagliptin group and 9% of the placebo group.[2]

In a similar group of 333 patients, another placebo-controlled trial studied three different doses (1 mg, 5 mg and 10 mg) of linagliptin and also included a glimepiride arm. All the patients continued to take metformin during the trial. After 12 weeks the active treatments had significantly reduced HbA1c from similar baseline values (see Table).[3] A longer term comparison found that after a year linagliptin 5 mg reduced HbA1c by 0.38% and glimepiride reduced it by 0.6%.

An 18-week trial studied linagliptin in combination with a sulfonylurea. Compared with placebo, the mean treatment difference was 0.47%.

Linagliptin has also been studied, in 1058 patients, as an addition to treatment with metformin and a sulfonylurea. While adding a placebo reduced the mean HbA1c by 0.1% after 24 weeks, linagliptin reduced it by 0.72%.[4]

Adding a drug which increases insulin secretion to the treatment of patients with diabetes increases the risk of hypoglycaemia. In patients taking metformin and a sulfonylurea, hypoglycaemia was reported in 22.7% when linagliptin was added and in 14.8% when a placebo was added.[4]

During monotherapy the adverse events in patients taking linagliptin included musculoskeletal problems, hypertension and headache.[1] Some patients may have increases in triglycerides and uric acid concentrations. Rare adverse events include hypersensitivity reactions and pancreatitis. A meta-analysis of cardiovascular events found no increased risk associated with linagliptin.

Animal studies have shown that linagliptin crosses the placenta and is excreted in breast milk.

Table **Effect of adding linagliptin, glimepiride or placebo to the treatment of patients with type 2 diabetes inadequately controlled by metformin** [3]

	TREATMENT				
	Placebo	Linagliptin 1 mg	Linagliptin 5 mg	Linagliptin 10 mg	Glimepiride 1 mg, 2 mg or 3 mg
Number of patients	71	65	66	66	65
Baseline HbA1c %	8.4	8.2	8.5	8.4	8.2
Change in HbA1c % after 12 weeks	+0.24	−0.14	−0.5	−0.42	−0.68

Linagliptin adds to the choice of drugs which can be considered when a patient's diabetes is not controlled by metformin and sulfonylureas. There seems little difference between the inhibitors of dipeptidyl peptidase, but linagliptin does not require a dose adjustment in patients with renal impairment.

T T manufacturer provided additional useful information

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

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

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

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

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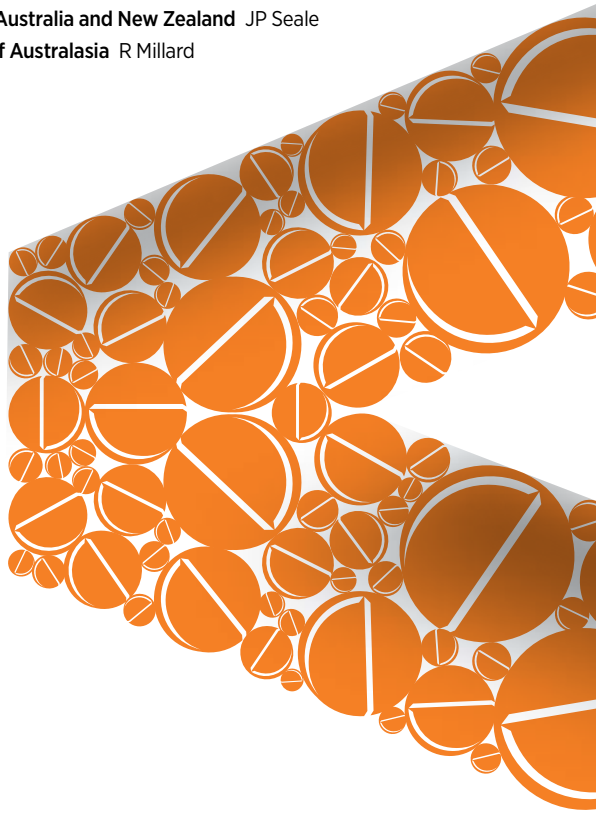

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