Australian Prescriber

Australian Prescriber is indexed by:
- EBSCO
- EMBASE/Excerpta Medica
- Iowa Drug Information Service
- Journal Citation Reports/Science Edition
- Science Citation Index Expanded (also known as SciSearch).

Typesetting
Blue Star Print, ACT

Printed in Australia by
Blue Star Print, ACT
22 Pirie Street FYSHWICK ACT 2609

Published by
NPS Better choices ▸ Better health
Independent. Not-for-profit. Evidence based.
Funded by the Australian Government Department of Health and Ageing.

Print Post Approved PP349181/00151 • ISSN 0312-8008

Australian Prescriber

VOLUME 33 | NUMBER 6 | AN INDEPENDENT REVIEW | DECEMBER 2010

CONTENTS

Editorial

Non-medical prescribing in Australia

***Lisa Nissen**, Associate Professor, School of Pharmacy, The University of Queensland, Brisbane, and **Greg Kyle**, Associate Professor, Discipline of Pharmacy, University of Canberra*

Key words: nurse prescribers, pharmacists, Pharmaceutical Benefits Scheme.

(Aust Prescr 2010;33:166–7)

The announcement in the 2009 federal budget to allow nurse practitioners and midwives access to the Pharmaceutical Benefits Scheme (PBS) and the Medicare Benefits Scheme,[1] and the subsequent announcement of a November 2010 start date,[2] has brought non-medical prescribing into the public arena. Non-medical prescribing is not a new concept in Australia as nurse practitioners, podiatrists and optometrists have been authorised to prescribe under various state legislations for some time. However, state legislation is not uniform in relation to authorisation or formulary. Midwives are currently seeking prescribing rights,[3] and other groups such as physiotherapists and pharmacists are likely to seek them in the future.

National consistency will be an important consideration in future legislation for non-medical prescribing, including the current nurse practitioner and midwife amendments. Work is currently underway to develop national consistency around prescribing models, incorporating a focus on patient safety and access to medicines. It appears likely that Australia will adopt models similar to those in the UK,[4] focused on an overarching collaborative practice framework between medical and non-medical prescribers. Additional models incorporating limited and broad protocol prescribing are likely to be included to cover the full scope of prescribing required in Australian practice.[5] Offering a range of prescribing models will allow individual practitioners to take more responsibility for their decisions, appropriate for their skill level and qualifications, in the context in which they are practising.

Clearly, there are other key considerations regarding implementation of non-medical prescribing in Australia. These have been highlighted in position papers from the Royal Australian College of General Practitioners[6] and the Pharmaceutical Society of Australia,[7] and include issues around training and credentialing, remuneration (including access to the PBS), access to medical records and professional indemnity. A key consideration surrounds the discrepancies in state legislation for non-medical prescribing which has been highlighted by the introduction of the National Registration and Accreditation Scheme.

National registration effectively abolishes state boundaries for the regulation of health professionals, but the state boundaries remain for prescribing. This situation may encourage health professionals in border areas to move to the side of the state border where their practice has greater scope. For example, an optometrist may move their practice from Coolangatta (Queensland) to Tweed Heads (New South Wales) and be able to prescribe glaucoma drops in a collaborative arrangement with an ophthalmologist. The resultant prescription would currently need to be dispensed in New South Wales to meet state legislation. Circumstances such as these could dramatically affect patient care and access to health professionals.

Formulary definition is another area of contention. Professions with a narrow scope of practice, for example optometrists or midwives, can have a formulary relatively easily defined – similar to the dental formulary of the PBS. However, defining a formulary for professions with a broad scope of practice (for example nurse practitioners or pharmacists) would prove more difficult. Trying to define a complete formulary for such professions would be akin to trying to define a formulary for general practitioners as a professional group. Individual practitioners could have an individual formulary defined but this would be unworkable for them and importantly the dispensing pharmacists. Two possible solutions are:

In this issue…

Prescribing rights are currently being extended to health professionals who are not medically qualified. While there may be benefits in having more prescribers, Lisa Nissen and Greg Kyle point out that training requirements and prescribing competencies need to be developed. Communication between prescribers will be essential and Debbie Rigby discusses how doctors and pharmacists can cooperate. There also needs to be cooperation between doctors and dentists and the letters pages show why this is important.

While there are restrictions on prescribing, there are few controls on the use of complementary medicines. Terri Foran includes them in her article on managing menopausal symptoms, while Geraldine Moses and Treasure McGuire review the potential interactions between these products and prescription drugs.

- allow the practitioner to self-define their formulary within their areas of demonstrated competence (this is the same as the UK non-medical prescribing model)
- define a range of formularies for various specialty areas, for example cardiology, respiratory, continence care, diabetes.

Training programs will need to reflect the scope of practice and whatever formulary restrictions are decided. This will be further influenced by the fact that there is currently no nationally consistent or agreed definition of what constitutes 'prescribing', or a framework of competencies, to guide what would be included in training programs and assessment. Currently, non-medical prescribers have a variety of profession-specific prescribing courses. It should be possible to develop a generic, profession-independent, prescribing course. Profession-specific modules could provide the basis of the prescribing course with the generic skill set common to all of them. This would ensure a consistent skill set across all non-medical prescribers. However, prescribing competencies would need to be developed to facilitate this process in Australia as there are currently no nationally defined prescribing competencies for any Australian prescriber, medical or non-medical.

Optometrists currently have a prescribing 'retro-fit' process that could be applied for any non-medical profession seeking prescribing rights. A 'top-up' course is available for current optometrists wanting to upgrade their qualification, and the entry level optometry course has been amended to ensure all future graduates would be automatically qualified as a prescriber. It is possible that other qualified non-medical prescribers (for example nurse practitioners) may also be required to undertake an upgrade course within a given time frame if the competency and training standards are raised above their current level. Many gaps exist in current education provision and this requires further and systematic development on a multidisciplinary basis. Profession-specific and profession-independent programs are required to generate future non-medical prescribers. These programs will be dependent on the non-medical prescribing models implemented in Australia.

Patient safety must be assured through ongoing review processes, for example as pharmacists currently do for medical prescribers. However, it is also important to allow health professionals to practise as health professionals and be personally accountable. The best prescriber for a given patient should depend on their skill set, not on which professional hat they wear.

References

1. Portfolio budget statements 2009–10. Budget related paper no. 1.10, Health and Ageing portfolio. 2009. www.health.gov.au [cited 2010 Nov 16]
2. Portfolio budget statements 2010–11. Budget related paper no. 1.11, Health and Ageing portfolio. 2010. www.health.gov.au [cited 2010 Nov 16]
3. Minister for Health and Ageing. A landmark day for Australian nurses and midwives [media release]. 2010 Mar 16. www.health.gov.au/internet/ministers/publishing.nsf/Content/mr-yr10-nr-nr050.htm?OpenDocument&yr=2010&mth=3 [cited 2010 Nov 16]
4. Barber N. Extended prescribing rights – the UK experience [editorial]. Aust Prescr 2009;32:118-9.
5. Crown J. Review of prescribing, supply and administration of medicines (the Crown report). London: Department of Health; 1999.
6. Royal Australian College of General Practitioners. RACGP position on independent non-medical practitioner prescribing – a statement of principles. 2009. www.racgp.org.au/policy/non_medical_prescribing.pdf [cited 2010 Nov 16]
7. Pharmaceutical Society of Australia. Principles for a national framework for prescribing by non-medical health professionals. 2009 Jun. www.psa.org.au/site.php?id=4170 [cited 2010 Nov 16]

Conflict of interest: none declared

Letters

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

Point-of-care testing

Editor, – We read Associate Professor Shephard's article with interest (Aust Prescr 2010;33:6–9), and wish to highlight emerging uses for point-of-care INR monitors in Australia. These have been trialled in various settings including:

- rural general practices[1] and community pharmacies[2], to improve warfarin safety in patients with limited access to pathology services
- patients' homes, to facilitate self-monitoring via a standardised training program[3*] and as a part of a multi-faceted post-discharge service provided by home medicines review accredited pharmacists[4*]
- within residential care facilities.[5]

These projects, conducted by the Unit for Medication Outcomes Research and Education (UMORE), have improved

patient outcomes and produced excellent stakeholder satisfaction. For example, the post-discharge service was recently associated with reduced rates of warfarin-related adverse events up to 90 days post-discharge.[4]

Patient self-monitoring is well established in Europe, where it is associated with improved anticoagulation control, enhanced patient convenience and adherence, fewer complications and improved survival in suitable patients.[6] Currently, only a small proportion of Australian patients taking warfarin perform self-monitoring, a situation that could be improved by a national training, quality assurance and support program.

We believe that appropriate use of point-of-care INR monitors outside traditional settings can potentially improve patients' quality of life and health outcomes and, as such, should be actively promoted and government-funded.

Gregory Peterson, Leanne Stafford, Luke Bereznicki, Ella van Tienen and Shane Jackson

Unit for Medication Outcomes Research and Education (UMORE), School of Pharmacy
University of Tasmania

* These programs were funded by the Department of Health and Ageing as part of the Fourth Community Pharmacy Agreement managed by the Pharmacy Guild of Australia

References

1. Jackson SL, Bereznicki LR, Peterson GM, Marsden KA, Jupe DM, Vial JH, et al. Accuracy and clinical usefulness of the near-patient testing CoaguChek S international normalised ratio monitor in rural medical practice. Aust J Rural Health 2004;12:137-42.
2. Jackson SL, Peterson GM, House M, Bartlett T. Point-of-care monitoring of anticoagulant therapy by rural community pharmacists: description of successful outcomes. Aust J Rural Health 2004;12:197-200.
3. Jeffrey EC, Bereznicki LR, Stafford L, Peterson GM. Evaluation of a clinical pathway to enable patient self-monitoring of anticoagulation. In: HAA Handbook and Final Programme. Adelaide: Haematology Society of Australia and New Zealand, Australian and New Zealand Society of Blood Transfusion, Australasian Society of Thrombosis and Haemostasis; 2009. p. 276.
4. Peterson GM, Stafford L, Bereznicki LR, van Tienen EC, Jackson SL, on behalf of the Project Team. The role of community pharmacy in post hospital management of patients initiated on warfarin. In: Pharmacy Practice Research Summit Program. Canberra: 2010. p.14.
5. Peterson G, Jackson S, Gee P, Bereznicki L, Bereznicki B, Fitzmaurice K, et al. Improving the management of warfarin in aged care facilities utilising an innovative IT solution. In: Australasian Pharmaceutical Science Association Conference. Manly: 2007.
6. Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, et al. Self-monitoring and self-management of oral anticoagulation. Cochrane Database Syst Rev 2010;4(Art. No.: CD003839):1-63.

Dental antibiotics

Editor, – I note the comments by Associate Professor Michael McCullough from the Australian Dental Association that antibiotics are not needed for the majority of dental infections (Aust Prescr 2010;33:71). However, access to public dentistry is limited and the wait for private dentists' appointments is often many weeks. Dental receptionists may tell patients who ring up for an appointment with a painful dental condition to go to the local doctor to get antibiotics. They often say 'because the dentist won't treat you unless you are on antibiotics'. Faced with a patient with a long and painful wait to see a dentist and a belief they have to be on antibiotics, it is impossible to not give a prescription. Why doesn't the dentist organise the antibiotics which 'must' be given?

Many of these patients may improve temporarily with anti-inflammatory drugs and perhaps the antibiotics. Then they decide they cannot afford to visit the dentist (if they were ever given an appointment at all).

Janet Watterson
General Practitioner
Pambula Medical Centre
Pambula, NSW

Associate Professor Michael McCullough, the author of the dental note, comments:

Dr Watterson's letter has prompted much discussion and much consternation amongst the members of the Dental Therapeutics Committee of the Australian Dental Association. She raises multiple concerns, including the under-resourced nature of public dentistry, the unprofessional activity of private dentists who do not offer prompt emergency appointments for their patients in pain, patients' expectations that antibiotics will cure toothache and their reluctance to seek appropriate definitive dental treatment, and the perceived high cost of dental treatment and the shortages of dentists, particularly in rural areas.

The vast majority of dental pain can be alleviated successfully by dental treatment without the need for systemic antibiotics. In many instances prescribing antibiotics could be seen as inappropriate. This has been one of the fundamental principles underlying dental education for the past several decades and permeates the recent Therapeutic Guidelines: Oral and Dental book made available to every member of the Australian Dental Association and to dental students. There are rare exceptions when a patient should take antibiotics before dental treatment and in these circumstances the antibiotics usually need to be taken immediately before treatment. Dentists are very capable of organising these prophylactic antibiotics. It would be inappropriate to rely on our medical colleagues to prescribe antibiotics many days – or even worse, weeks – before dental treatment without a dentist first examining and diagnosing the patient's dental problem.

Although a patient's pain may improve temporarily with anti-inflammatory drugs and antibiotics, this is not definitive treatment and it has the potential to lead to both the development of antibiotic resistance and a disastrous outcome for the patient. Every large tertiary hospital in Australia has cases requiring hospitalisation for extensive, potentially lethal, head and neck infections of dental origin. One survey reported 44 patients in one calendar year with 40% of these patients requiring intubation, high dependency or intensive care and prolonged hospitalisation. The majority of these patients had previously taken one or more courses of antibiotics to unsuccessfully treat their dental pain.[1]

The perception that dentists will not treat patients unless they are taking a course of antibiotics is fundamentally wrong. Any dentist who believes this, or allows their staff to portray this attitude, needs to re-think their practice and attend further continuing education courses. Moreover, under the Dental Board of Australia's recently released Guidelines for Mandatory Notifications[2] it is stated that: '…the National Law defines 'notifiable conduct' as where a practitioner has … placed the public at risk of harm because the practitioner has practised the profession in a way that constitutes a significant departure from accepted professional standards'. It could well be argued that this behaviour is a significant departure from accepted professional standards.

The responsibility for the treatment of dental pain should lie entirely with the dentists. However, in reality there are large numbers of patients who seek medical care for their dental pain. Developing a relationship between local doctors and dentists and creating a dialogue such that patients in dental pain presenting to doctors can be helped to make appropriate emergency appointments with the local dentists will go a long way towards decreasing inappropriate treatment. Furthermore, dentists should also provide feedback to doctors on the treatment provided, as well as information regarding any patients who fail to attend appointments and delay seeking treatment. Such a dialogue would be in the best interests of the patients and would perhaps go a long way towards altering perceptions regarding the shortages of availability of dentists and the affordability of dental treatment. A very positive suggestion would be for local doctors and dentists to meet to address the problems. The Australian Dental Association via its state branches and local groups would probably be very pleased to facilitate such meetings.

To alleviate the shortage of dentists, there has been a significant increase in dental schools in Australia (from five in 2005 to the current number of nine). All new graduating dentists will be taught that, in the vast majority of patients, dental pain can be treated with dental treatment, without the need for either pre-treatment, or post-treatment antibiotics.

References

1. Uluibau IC, Jaunay T, Goss AN. Severe odontogenic infections. Aust Dent J 2005;50:S74-81.
2. Dental Board of Australia. Guidelines for mandatory notifications. www.dentalboard.gov.au/Codes-and-Guidelines.aspx [cited 2010 Nov 16]

Multiresistant organisms at the front line

Editor, – I read the dental note (Aust Prescr 2010;33:71) about not using amoxycillin as the first drug of choice for oral infection to reduce the prevalence of multiresistant bacteria, for example life-threatening *Streptococcus pneumoniae*.

I am a dentist and we have always been told that amoxycillin is the best and safest antimicrobial when encountering oral infection. So what will be the next best thing?

Shahriar Sanati
Dentist
Tuggerah, NSW

Associate Professor Michael McCullough, Chair, Therapeutics Committee, Australian Dental Association, comments:

It is true that for many years dentists were told that amoxycillin was the best and safest antibiotic for most dental infections. However, this idea has been considerably challenged over the past several decades and has led to the current concept that penicillin is the best choice as first option. These concepts are clearly outlined in the Therapeutic Guidelines: Oral and Dental.

Unfortunately, there is probably not going to be a 'next best thing', so we need to use our currently available antimicrobial medications judiciously.

Bisphosphonates

Editor, – Bisphosphonates are increasingly being prescribed for a number of clinical conditions. In the dental literature there have been a number of red flags raised, notably by Professor A Goss (Aust Prescr 2007;30:96–7), concerning the incidence of osteonecrosis of the jaw and bisphosphonate use, particularly when administered intravenously.

Would it not be timely for our medical colleagues to advise patients of this risk so that patients will, when they are taking bisphosphonates, inform their dental practitioners.

In my practice we routinely ask patients at each visit regarding all medications being taken, by prescription and otherwise. However, even with that regimen a number of patients have not bothered to mention that they are taking a bisphosphonate, as they did not think it mattered. It is too often the case that as far as patients are concerned medicines prescribed by their doctor will have no impact upon any dental care which they might require.

This is of course not the case and for this reason I appeal to our medical colleagues to be proactive in this regard.

JF Walsh
Dental Surgeon
Kojonup Dental Clinic
Kojonup, WA

New oral anticoagulants

Editor, – The article by Professor Gallus (Aust Prescr 2010;33:42–7) discussed the clinical applications of the new oral anticoagulants – rivaroxaban and dabigatran. In those patients who had had hip or knee replacements, the new drugs were started either 6–8 hours after wound closure or 1–4 hours after surgery. Would Professor Gallus kindly give his advice to orthopaedic surgeons for those patients who have had a previous deep vein thrombosis or who possess one of the inherited thrombotic tendencies such as Factor V Leiden mutation.

JL Raven
Clinical haematologist and Consultant physician
Waikiki Private Hospital
Waikiki, WA

Professor Alex Gallus, author of the article, comments:

Patients with a previous deep vein thrombosis or pulmonary embolism pose special problems for surgeons because of their increased risk of a postoperative recurrence. After recent venous thromboembolism, elective surgery should be delayed for at least 3–6 months to permit the initially high risk for a recurrence to subside. Beyond 3–6 months, individual practice varies, since there is little good evidence to guide the clinician.

One common approach is to add intermittent pneumatic leg compression to low molecular weight heparin prophylaxis, and start warfarin once the postoperative bleeding risk allows. The duration of warfarin treatment would then depend on whether the patient's history justifies long-term therapy. It is not yet known if prophylactic doses of the new oral anticoagulants can replace warfarin for the secondary prevention of venous thromboembolism. In the dabigatran and rivaroxaban studies of prophylaxis after joint replacement, 2–4% of patients reported a history of venous thrombosis. This was too few for meaningful subgroup analyses of relative efficacy.

There is substantial evidence that heterozygosity for Factor V Leiden or the G20210A prothrombin gene mutation, without a personal history of thromboembolism, does not raise the risk of postoperative thrombosis above the average. In these patients, standard prophylactic dosing regimens should be sufficient. Risk associated with homozygosity or double heterozygosity, however, is well above average and would need more intense and longer prophylaxis.

Safety of heparins for venous thromboembolism prophylaxis

Editor, – Further to the article by the NSW Therapeutic Advisory Group (Aust Prescr 2009;32:108–12), we would like to draw your attention to the recently updated position statement 'Safe use of heparins and oral anticoagulants for venous thromboembolism prophylaxis in adults' (at www.nswtag.org.au).

The position statement aligns with the National Health and Medical Research Council 2009 Clinical Practice Guideline for the prevention of venous thromboembolism in patients admitted to Australian hospitals, and includes updated information on oral anticoagulants approved for venous thromboembolism prophylaxis and assessing renal function.

With growing Australian and international encouragement for instituting venous thromboembolism prophylaxis systems in hospitals, it can be expected that an increased number of inpatients will be prescribed venous thromboembolism prophylaxis.

However, heparins (even in a low dose) and oral anticoagulants carry a risk of causing bleeding from any site, especially in patients at increased risk of bleeding from other causes such as concurrent administration of some medicines, some clinical conditions and some surgical and anaesthetic procedures. Careful clinical management of patients at risk of bleeding is required to minimise the risk and severity of bleeding related to venous thromboembolism prophylaxis.

Six steps for safe provision of venous thromboembolism prophylaxis are outlined:

Step 1: Identify patients requiring venous thromboembolism prophylaxis

Step 2: Assess for bleeding risk and contraindications

Step 3: Assess for special precautions

- 3. 1 Renal impairment
- 3. 2 Concomitant medicines
- 3. 3 Determine if neuraxial (spinal/epidural) anaesthesia is planned
- 3. 4 Obesity

Step 4: Select the most appropriate heparin or anticoagulant agent

Step 5: Determine appropriate timing of venous thromboembolism prophylaxis

Step 6: Monitor for adverse events.

While this document aims to guide clinical practice, it is not intended to replace clinician judgement. Many decisions for venous thromboembolism prophylaxis need to be made on an individual patient basis. These are highlighted clearly in the text.

Paul Seale
Chair

Gillian Campbell
Executive Officer

NSW Therapeutic Advisory Group
Darlinghurst, NSW

Managing menopausal symptoms

***Terri Foran**, Sexual Health Physician, Taylor Square Private Clinic, Darlinghurst, and Lecturer, School of Women's and Children's Health, University of New South Wales, Sydney*

Summary

Until the mid 1990s, hormone therapy was seen as not only a safe means of relieving troublesome menopausal symptoms but as a way of preserving youth and vitality. Adverse findings from a number of studies in the 1990s cast doubt on some of the earlier claims, but it was the publication of the Women's Health Initiative study in 2002 that resulted in a complete reappraisal of the principles of menopause management.

Key words: bioidentical hormones, hot flushes, libido, urogenital symptoms.

(Aust Prescr 2010;33:171–5)

Introduction

Menopause, literally the 'end of menstruation', marks an important transition in a woman's life and occurs in Australia at an average age of 51 years. Menopausal symptoms, which may commence even before the last menstrual period, include vasomotor symptoms, urogenital problems, psychological changes, sleep disturbance and decreased libido. Managing patients with these symptoms can be a challenge.

Vasomotor symptoms

Vasomotor symptoms include hot flushes, night sweats and formication, which is a particularly unpleasant sensation that feels like ants crawling on the skin. It is estimated that up to 80% of women experience vasomotor symptoms around the time of menopause with an average duration of 5–6 years.[1] However, one in four women will still experience significant vasomotor symptoms well into their sixties and in 10% these will persist for life.

Lifestyle modification and natural therapies

Regardless of any other therapies, education and lifestyle advice are integral to effective menopause management. Since smoking has the added impact of increasing the severity of vasomotor symptoms and increasing the risk of osteoporosis,[2] menopause provides a good opportunity to discuss smoking cessation.

Dietary modification and the use of herbal supplements are avenues commonly explored by women seeking a more natural approach to menopause management. For some women with milder symptoms, avoidance of known vasomotor triggers such as alcohol, hot drinks and spicy foods may be the only intervention required. Although a diet rich in plant oestrogens such as those found in foods like soy, chickpeas, lentils and flaxseed is likely to be a more healthy option, there is unfortunately no clear evidence that they improve vasomotor symptoms for the majority of women.[3]

Red clover extract has been widely used for the relief of vasomotor symptoms, but there is no convincing evidence that it is any more effective than placebo.[4,5] A number of small clinical trials investigating other herbal products – such as dong quai, *Ginkgo biloba*, wild yam and *Vitex agnus castus* – have also shown no benefit over placebo.

Black cohosh is a herbal compound which appears to have some serotonergic activity. Its use for menopausal symptoms remains controversial, with some studies indicating significant improvement while others have failed to demonstrate any benefit over placebo. Black cohosh preparations vary in dose and potency and this further complicates their evaluation as a treatment. Since at least some reviews indicate evidence for its effectiveness,[6] it may be worth trying in those women who are looking for a natural alternative to oestrogen therapy. In my experience it is relatively safe to use and is available as an over-the-counter product. The commonest adverse effect is gastrointestinal upset but there have been reports of idiosyncratic liver failure[7] and all black cohosh products marketed in Australia now carry a warning to this effect.

Hormone therapy

Women using systemic oestrogen therapy can expect a 75% reduction in the frequency of hot flushes and an 87% reduction in their severity.[8] However, there are risks associated with hormone therapy. Most of the contemporary evidence is derived from the Women's Health Initiative trial data.[9] Although it is the oestrogen which controls menopausal symptoms, women with a uterus also require progestogen for at least 10 days per month to prevent endometrial hyperplasia (Table 1). For such combined therapy there appears to be an increased risk of coronary artery disease, thromboembolism and stroke from the time of initiation. However, some argue that the risk of heart disease is less if therapy is commenced before the age of 60.[10–12]

An increase in cases of breast cancer was also seen after 4–5 years of combined hormone therapy, with eight additional cases per 10 000 women years. Therapy with oestrogen alone appears to be associated with fewer risks, with an increased risk of stroke being the sole adverse finding after seven years.[13]

Table 1 *

Progestogens used in combined therapy for menopausal symptoms

Cyclical therapy Use for at least 10 days per month until 12–18 months after last menses. Allows for scheduled monthly bleed.	Dydrogesterone 10 mg Medroxyprogesterone 5–10 mg Norethisterone/norethisterone acetate 0.7–2.5 mg
Continuous therapy Defer until 12–18 months after last menses. No scheduled bleed.	Dydrogesterone 5 mg Medroxyprogesterone 2.5–5 mg Norethisterone/norethisterone acetate 0.35–1 mg
Progestogen intrauterine device	Releases 20 microgram levonorgestrel daily

* adapted from 'Hormone replacement – oestrogen and progestin dosage schedule'. National Prescribing Service. 2009 Aug. www.nps.org.au/ppr_47_insert [cited 2010 Nov 16]

A variety of hormonal preparations and different delivery systems are available in Australia. As a general principle the lowest dose of oestrogen should be prescribed that adequately controls symptoms, with the appropriateness of continuing therapy assessed at 6–12 month intervals. Typical starting doses for oestrogen are shown in Table 2, but even at the six-month review it may be worthwhile attempting to reduce the dose further.

Within two months of commencing therapy approximately 80% of women will achieve adequate symptom relief.[14] With the remaining 20%, it may be useful to explore an alternative delivery system before increasing the dose. Older women who still require therapy may find their symptoms are controlled on half the standard starting dose.

Tibolone is a steroid which has oestrogenic, progestogenic and androgenic activity. The standard dose is 2.5 mg although a half dose could be considered in older patients. Once a decision has been made to commence hormone therapy, the approach to treatment will be influenced by many factors (Fig. 1).

Transdermal progesterone cream has been used for the management of menopausal symptoms since the 1970s. It is minimally absorbed through the skin and there is no good evidence for its usefulness in relieving flushes, or in improving mood, libido or lipid profile.[15]

Other pharmacological therapies for vasomotor symptoms

When hormone therapy is contraindicated, or when women choose not to use it, low-dose selective serotonin or noradrenaline reuptake inhibitors may be considered. In short-term trials, they have been shown to reduce the number and severity of hot flushes by approximately 60%.[16,17] A quarter to a half of the antidepressant dose is recommended, and in fact higher doses have the potential to make vasomotor symptoms worse. However, adverse effects such as breast tenderness and sexual dysfunction may still limit the use of these drugs in some women even at such low doses. Venlafaxine and paroxetine appear to be the most effective of this class for this purpose. Paroxetine should be avoided in breast cancer survivors on tamoxifen since liver enzyme inhibition may render tamoxifen less effective.[18]

Clonidine and high-dose progestogens also seem to be effective at reducing troublesome vasomotor symptoms in some women, but adverse effects tend to limit their widespread use. A number of small trials[19] have indicated that gabapentin and pregabalin may also be effective in controlling hot flushes, but expense and limited clinical experience has meant that their use is usually restricted to those women with significant symptoms who have failed to respond to other therapies.

Bioidentical hormone therapy

Compounded bioidentical hormone therapy has been widely promoted in Australia. These preparations are said to have been derived only from natural products such as wild yam and soy and to deliver steroids identical to those made by the woman's own body. Advocates claim the ability to titrate the preparation to the woman's own individual hormonal needs, guided by salivary or blood tests.

Most compounded preparations deliver a combination of oestriol and oestradiol. Other hormones such as oestrone, progesterone, testosterone and dehydroepiandrosterone may be added.

The hormone therapy is delivered by means of a dissolvable

Table 2 *

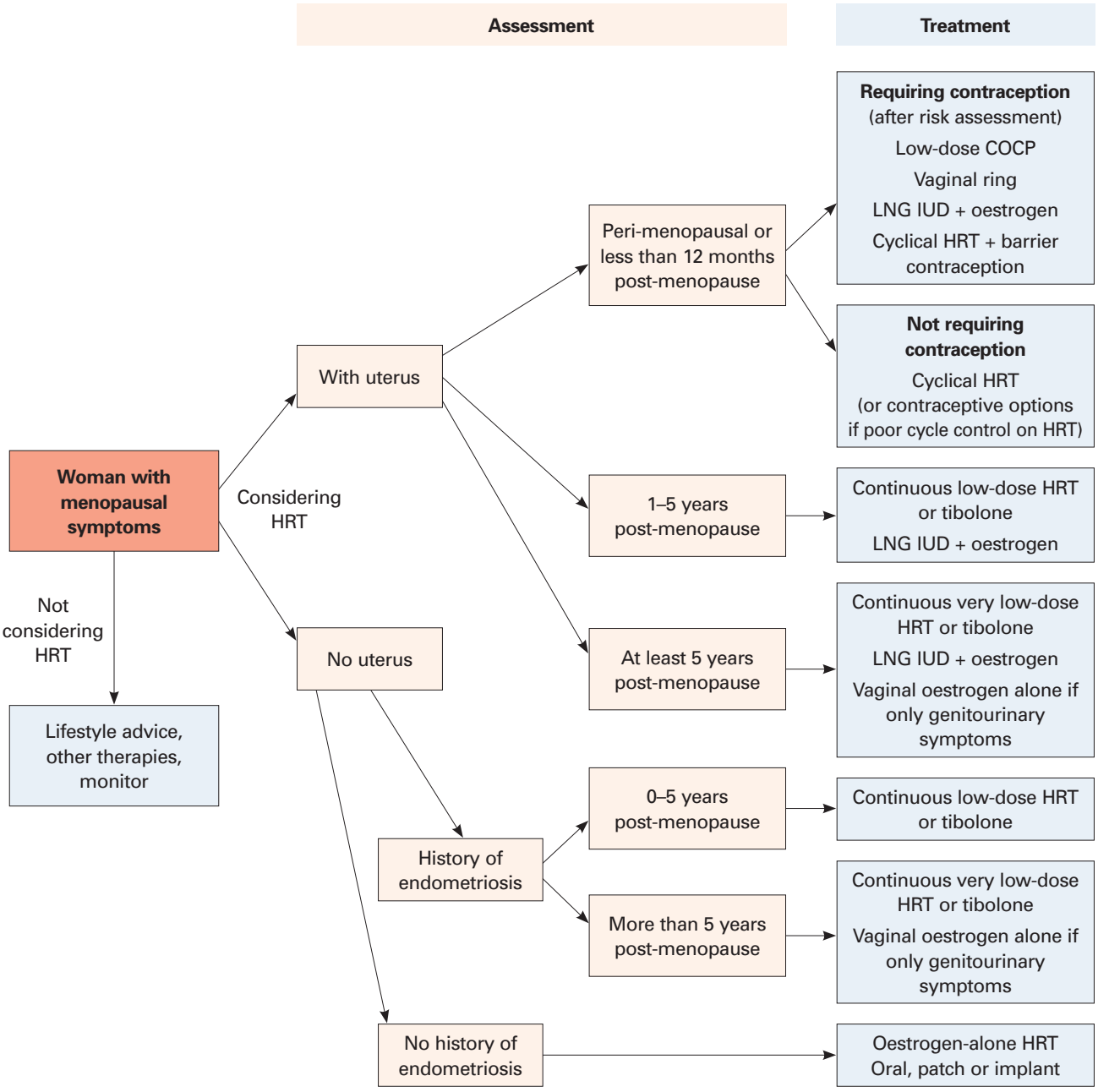
Typical starting doses of oestrogens for menopausal symptoms

Oral	Conjugated equine oestrogens 0.3–0.625 mg Oestradiol/oestradiol valerate 1–2 mg
Transdermal (over 24 hours)	Oestradiol 25–50 microgram Oestradiol gel 1 mg/g
Sub-dermal implant (usually reserved for women who have had a hysterectomy)	Oestradiol 50 mg

* adapted from 'Hormone replacement – oestrogen and progestin dosage schedule'. National Prescribing Service. 2009 Aug. www.nps.org.au/ppr_47_insert [cited 2010 Nov 16]

Fig. 1

Implementing hormone therapy for menopausal symptoms in women with no contraindications



HRT hormone replacement therapy
COCP combined oral contraceptive pill
LNG IUD levonorgestrel-releasing intrauterine device

lozenge (troche) or a transdermal cream. There is no doubt that many women find these preparations effectively relieve their menopausal symptoms. The problem is that although bioidentical hormones are often perceived by women as a safer alternative to conventional hormone therapy, there is actually no evidence for this, particularly regarding long-term safety.[20] One emerging concern is that the natural progesterone used in many bioidentical regimens to protect the endometrium may not be particularly effective, especially with long-term use. There have been a number of reports recently of endometrial hyperplasia and endometrial cancer in users.[21]

Urogenital symptoms

Unlike vasomotor symptoms, urogenital symptoms such as vaginitis, dyspareunia, cystitis and incontinence tend to worsen as a woman grows older.

Oestrogen

Pooled data from several randomised controlled trials indicate that oestrogen improves genital symptoms regardless of the route of administration.[22] Vaginal oestrogen is the preferred delivery system for women whose symptoms are primarily urogenital. There is minimal systemic absorption and when vaginal oestrogen is used at the recommended dosages progestogen cover is not necessary in women with a uterus. Even this small absorbed dose may however compromise therapy in breast cancer survivors receiving aromatase inhibitors, such as anastrozole.

Vaginal oestrogen may also be useful in the 27% of women who still experience vaginal symptoms when using low-dose systemic hormone therapy.[23] Oestradiol is more potent than oestriol and will therefore provide a more rapid clinical effect when used topically. Vaginal tablets tend to be better tolerated than pessaries and creams since they result in less vaginal discharge. As a therapeutic option vaginal oestrogen remains very much underused, particularly in women troubled by recurrent urinary tract infections and incontinence.

Vaginal moisturisers and lubricants

For women who cannot, or do not wish to, use even low-dose vaginal oestrogen, polycarbophil vaginal moisturisers have been shown to improve vaginal pH and normalise vaginal cytology.[24]

Lubricants can also be useful for augmenting natural lubrication during intercourse. Silicone lubricants offer particular advantages for the older couple since they do not absorb so easily into the skin.

Libido and desire

Painful sex is a potent inhibitor of desire and local oestrogen therapy may be all that is required in some women. A recent review of postmenopausal trials indicated that conventional oestrogen hormone therapy tended to increase sexual desire, arousal and satisfaction.[25]

A gradual decline in androgen levels from the mid-thirties may lead to symptoms such as decreased libido and a lack of energy in some women. Several small studies[26–8] suggest that the androgenic component of tibolone may improve both sexual interest and general well-being. However, the role of androgens in the treatment of postmenopausal loss of libido remains controversial. There are currently no preparations licensed for use in women across Australia, though a low-dose transdermal testosterone cream is available on prescription in Western Australia. Androgen therapy should never be used indiscriminately and only after discussion with the patient about potential adverse effects.

There is also no doubt that study after study has shown that sexual satisfaction is most closely correlated with satisfaction with the relationship. Any pharmacological therapy may be more effective if combined with couple counselling.

Conclusion

The promotion of a healthy lifestyle forms an integral part of an overall approach to menopause management. The findings of the 2002 Women's Health Initiative study profoundly affected long-held notions as to the benefits and safety of menopausal hormone therapy, though it remains a useful option for those with significant symptoms. Vaginal oestrogen therapy in particular provides excellent relief of genitourinary symptoms with very few associated risks. Although many women regard complementary therapies as a safer alternative to conventional medical treatment, there is conflicting evidence as to their effectiveness and long-term safety. The application of an evidence-based approach to decision-making should assist both clinician and patient to make the choices that are most appropriate to a woman's individual needs.

References

1. Col NF, Guthrie JR, Politi M, Dennerstein L. Duration of vasomotor symptoms in middle-aged women: a longitudinal study. Menopause 2009;16:453-7.
2. Greendale G, Gold EB. Lifestyle factors: are they related to vasomotor symptoms and do they modify the effectiveness or side effects of hormone therapy? Am J Med 2005;118(Suppl 12B):148-54.
3. Lethaby AE, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for vasomotor menopausal symptoms. Cochrane Database of Systematic Reviews 2007, Issue 4.
4. Knight DC, Howes JB, Eden JA. The effect of Promensil, an isoflavone extract, on menopausal symptoms. Climacteric 1999;2:79-84.
5. Baber RJ, Templeman C, Morton T, Kelly G, West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. Climacteric 1999;2:85-92.
6. Geller SE, Studee L. Contemporary alternatives to plant estrogens for menopause. Maturitas 2006;55(Suppl 1):S3-13.
7. ADRAC. Hepatotoxicity with black cohosh. Aust Adv Drug React Bull 2006;25:6.
8. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database of Systematic Reviews 2004, Issue 4.
9. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
10. Grodstein F, Manson JE, Stampfer MJ. Hormone therapy and coronary heart disease: the role of time since menopause and age at hormone initiation. J Womens Health (Larchmt) 2006;15:35-44.
11. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report. Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med 2006;21:363-6.

12. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-77.
13. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in post menopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-12.
14. Birkhauser MH, Panay N, Archer DF, Barlow D, Burger H, Gambacciani M, et al. Updated practical recommendations for hormone replacement therapy in the peri- and postmenopause. Climacteric 2008;11:108-23.
15. Wren BG, Champion SM, Willets K, Manga RZ, Eden JA. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for menopausal women. Menopause 2003;10:13-8.
16. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-63.
17. Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, Bunnell C. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol 2005;23:6919-30.
18. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ 2010;340:c693.
19. Butt DA, Lock M, Lewis JE, Ross S, Moineddin R. Gabapentin for the treatment of menopausal hot flushes: a randomized controlled trial. Menopause 2008;15:310-8.
20. The Jean Hailes Foundation for women's health. 'Bio-identical' Hormones [fact sheet]. Updated 2009 Dec. www.jeanhailes.org.au/images/stories/Education/Documents/info/bioidentical_hormones.pdf [cited 2010 Nov 16]
21. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with 'bioidentical' hormone replacement therapy. Med J Aust 2007;187:244-5.
22. Rymer J, Morris EP. Extracts from 'Clinical evidence': Menopausal symptoms. BMJ 2000;321:1516-9.
23. Notelovitz M. Urogenital aging: solutions in clinical practice. Int J Gynecol Obstet 1997;59(Suppl 1):S35-9.
24. Van der Laak JA, De Bie LM, de Leeuw H, de Wilde PC, Hanselaar AG. The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerised cytometry. J Clin Pathol 2002;55:446-51.
25. Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Whallen K, Notelovitz M. The effects of menopausal hormone therapies on female sexual functioning: review of double-blind randomized controlled trials. Menopause 2004;11:749-65.
26. Tax L, Goorissen EM, Kicovic PM. Clinical profile of Org OD 14. Maturitas 1987:Suppl 1:3-13.
27. Castelo-Branco C, Vicente JJ, Figueras F, Sanjuan A, Martínez de Osaba MJ, Casals E, et al. Comparative effects of estrogens plus androgens and tibolone on bone, lipid pattern and sexuality in postmenopausal women. Maturitas 2000;34:161-8.
28. Egarter C, Huber J, Leikermoser R, Haidbauer R, Pusch H, Fischl F, et al. Tibolone versus conjugated estrogens and sequential progestogen in the treatment of climacteric complaints. Maturitas 1996;23:55-62.

Dr Foran is a participant in advisory committees for Schering Plough Australia (now Merck Sharp & Dohme) and Bayer Schering, and has accepted honoraria and educational grants for presentations at educational sessions sponsored by Bayer Schering and Schering Plough. She is a sub-investigator for the Women's Health Research Institute of Australia, Randwick, which conducts pharma-sponsored clinical trials.

There is information for consumers with this article at www.australianprescriber.com

Self-test questions

The following statements are either true or false (answers on page 198)

1. When prescribing hormone therapy, women with a uterus require progestogen in addition to oestrogen.
2. Vaginal oestrogen should not be given to women receiving aromatase inhibitors.

RADAR

The latest edition of NPS RADAR reviews denosumab for postmenopausal osteoporosis, and exenatide for type 2 diabetes mellitus.

To read the full reviews go to www.nps.org.au/radar

Message to all 2010 graduates in medicine, pharmacy and dentistry

If you are graduating in Australia this year and you wish to continue receiving *Australian Prescriber* to assist with your postgraduate training, please complete and send in the form on the inside back cover of this issue, or register online at www.australianprescriber.com

Medicines Australia Code of Conduct: breaches

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

The latest report[2] reflects the first year of operation of the 16th edition of the Code. As usual, most complaints about promotional activity were made by rival pharmaceutical companies or the Medicines Australia Monitoring Committee. Only about half of the complaints resulted in a breach of the Code being found. Table 1 shows the complaints where at least one breach was identified and more details can be found in the full report.[2]

References

1. Medicines Australia. Code of Conduct. 16th ed. 2009. www.medicinesaustralia.com.au [cited 2010 Nov 16]
2. Medicines Australia. Code of Conduct Annual Report 2010. www.medicinesaustralia.com.au [cited 2010 Nov 16]

Table 1

Breaches of the Code of Conduct July 2009 – June 2010

Company	Brand (generic) name	Material or activity	Sanction imposed by Code of Conduct Committee
Allergan	Botox (botulinum toxin)	Promotional material	$100 000 fine Withdraw material Corrective letter
Biogen Idec	Tysabri (natalizumab)	Promotional material	$75 000 fine Withdraw material Corrective advertisement
Boehringer Ingelheim	Mobic (meloxicam)	Advertorial	$50 000 fine Corrective advertisement
CSL	Human papillomavirus vaccine	Information for the public	$1000 fine
	Various	Starter packs	$1000 fine
Genzyme	Renagel (sevelamer)	Patient education leaflet	$25 000 fine Withdraw material Corrective letter
GlaxoSmithKline	Valtrex (valaciclovir)	Advertising to the public	$150 000 fine reduced to $20 000 on appeal
Merck Sharp & Dohme	–	Hospitality for specialists	$20 000 fine
	–	Hospitality for specialists	$40 000 fine
	–	Hospitality for specialists	$50 000 fine reduced to $10 000 on appeal
Pharmalink	Pletal (cilostazol)	Hospitality for specialists and general practitioners	$50 000 fine
sanofi-aventis	Copaxone (glatiramer)	Promotional material	$25 000 fine Withdraw material Corrective letter
	Clexane (enoxaparin)	Promotional material	Corrective letter
Schering Plough	Olmetec (olmesartan)	Promotional material	$35 000 fine Withdraw material
Servier	Coversyl (perindopril)	Promotional material	$100 000 fine Withdraw material Corrective letter (Requirement for corrective advertisement removed on appeal)

Drug interactions with complementary medicines

***Geraldine M Moses**, Senior Clinical Pharmacist, Mater Health Services, Brisbane, and **Treasure M McGuire**, Assistant Director of Pharmacy, Mater Health Services, and Conjoint Senior Lecturer, School of Pharmacy, University of Queensland, Brisbane, and Associate Professor of Pharmacology, Faculty of Health Sciences and Medicine, Bond University, Queensland*

Summary

Health professionals are expected to be familiar with common and clinically significant complementary medicine interactions or at least know where to look them up. Knowing the dynamic and kinetic interactions associated with commonly used complementary medicines helps to identify the risk of drug interactions. Although information on complementary medicine interactions is not readily provided by the manufacturers, evidence is available by way of case reports, independent research and web-based resources, which have increased in recent years. Collectively, these data make interactions with complementary medicines largely predictable and therefore preventable.

Key words: drug interactions, St John's wort.

(Aust Prescr 2010;33:177–80)

Introduction

The Therapeutic Goods Administration refers to complementary medicines as 'medicinal products containing herbs, vitamins, minerals, nutritional supplements, homoeopathic medicines, traditional medicines and certain aromatherapy products'.[1] In Australia, complementary medicines are largely regulated as unscheduled medicines, and are usually self-selected.

Complementary medicines are very popular among Australians, with surveys indicating that up to 60% of people use at least one complementary medicine on a regular basis. However, about 50% of consumers also report using a conventional medicine on the same day as their complementary medicine.[2,3] It is not surprising, therefore, that healthcare professionals and consumers alike are concerned about the potential for drug interactions between these medicines.

As so many Australians use complementary medicines, including children, the elderly, patients with chronic disease, mental health disorders and cancer, it is important that prescribers always ask what complementary products their patients are taking in addition to any conventional medicines. Knowing this, and extrapolating reported pharmacodynamic and pharmacokinetic outcomes, can help predict potential drug interactions.

Polypharmacy

Complementary medicines are frequently used in the context of polypharmacy. A study of 3070 elderly people found that 74.2% took at least one prescription drug and one complementary medicine, with 32.5% of them using three or more prescription medicines with three or more complementary medicines.[4] This translates to an increased risk of drug interactions. In a study of 458 US Veterans' Administration patients, 197 of them reported taking complementary medicines combined with prescription medicines. Of these patients, 45% had potential for interactions, which was rated as serious in 6% of patients.[5] In another study which interviewed 3000 people (aged 57–85) about prescription, over-the-counter and complementary medicine use, 4% of them were potentially at risk of a major drug–drug interaction.[6] It has been suggested that once a patient is on eight or more medicines, regardless of origin, there is a 100% chance of a drug interaction occurring.[7]

Drug interactions

As with other drugs, complementary medicine interactions can be broadly classified by their mechanism, that is, pharmacodynamic and pharmacokinetic. The former are due to overlap of pharmacological actions, while the latter result from changes in absorption, distribution, metabolism or excretion.

Risk factors for significant complementary medicine interactions are the same as for conventional medicines. These include patient characteristics (such as extremes of age, frailty, female gender, cognition, comorbities and genetic disposition) and medication factors (such as high medication burden, recent changes in medicines, drugs with a low therapeutic index and limited elimination pathways).

Due to their complex chemical structure, herbal medicines are prone to interactions via the oxidative cytochrome P450 system or the efflux drug transporter P-glycoprotein.[8,9] *In vitro* assays, using human tissue or cell lines, are frequently used to determine whether a herb affects these enzymes.[10] However, *in vitro* findings do not necessarily correlate with what happens in the human body. As several herbal medicines and many prescription drugs are substrates, inducers or inhibitors of CYP isoenzymes or P-glycoprotein, interactions can ensue when they

are used concomitantly.[9] A classic example is St John's wort, which has kinetic interactions with a wide range of drugs via the induction of CYP1A2, CYP3A4, CYP2C9 and P-glycoprotein.[11] This lowers the concentration of the concomitant drug.

Table 1 shows selected documented interactions which have been chosen based on a composite of:

- the most frequently used complementary medicines in Australia, from survey and sales data[12]
- interactions with serious or clinically significant outcomes.

Table 1 categorises interactions by their possible outcome, severity, supporting evidence and proposed mechanism. Generic guidance on interaction management is given in the key, within the definitions of severity (major, moderate, minor). Certain therapeutic drug classes appear repeatedly in the table such as antiplatelet drugs, anticoagulants, antidepressants, antihypertensives, hypoglycaemics, immunosuppressants, antiretrovirals and hormones. Health professionals should monitor patients closely when a complementary medicine is taken concomitantly with these drugs.

Table 1

Evidence-based complementary medicine interactions [8,11,13,14]

This table shows complementary medicines with at least one 'major' interaction. For the full version of this table, see this article online at www.australianprescriber.com

Complementary medicine	Interacting drug	Possible outcome	Severity and level of evidence*	Proposed mechanisms/ comment
Evening primrose oil	Antiplatelet drugs, warfarin	↑ drug effect	**Major**, level B	Contains gamma-linolenic acid, probable anticoagulant
Garlic	Contraceptives, oral	↓ drug effect	Moderate, level D	Induces CYP3A4
	Saquinavir/non-nucleoside reverse transcriptase inhibitors	↓ drug levels and effect	**Major**, level B	Induces CYP3A4
	Antiplatelet drugs, warfarin	↑ bleeding risk	Moderate, level D	Theoretical antiplatelet activity
Ginkgo	Anticonvulsants	↑ seizure risk	Moderate, level D	Large amounts of ginkgotoxin can cause neurotoxicity
	Warfarin, antiplatelet drugs	↑ bleeding risk	**Major**, level D	Antiplatelet activity after several weeks
	CYP2C9 substrates e.g. glipizide, warfarin, celecoxib	↑ substrate levels	Moderate, level D	Inhibits CYP2C9 activity
	CYP1A2, CYP2C19, CYP2D6 and CYP3A4 substrates	↑ substrate levels	Moderate, level B	Potentially inhibits these enzymes
	Hypoglycaemic drugs	↑ ↓ drug effect	Moderate, level B	Variably affects blood glucose concentrations
Glucosamine	Warfarin	↑ bleeding risk	**Major**, level D	Several case reports of increased INR
Hawthorn	Calcium channel blockers, nitrates, phosphodiesterase inhibitors	↑ drug effect	**Major**, level D	Additive vasodilator effects
	Digoxin, beta blockers	↑ drug effect	**Major**, level D	Additive effects on heart rate and/or blood pressure. Hawthorn has cardiotonic effects.
Kava	CNS depressants	↑ drug effect	**Major**, level A	Additive somnolence
	CYP1A2, CYP2D6, CYP2C9, CYP2E1, CYP3A4 substrates	↑ substrate levels	Moderate, level B	Kava potentially inhibits these enzymes
	P-glycoprotein substrates	↑ substrate levels	Moderate, level D	
St John's wort	Alprazolam	↓ drug levels and effect	**Major**, level B	Increased clearance; half-life reduced by 50%
	Amitriptyline	↑ drug effect	**Major**, level B	Increased risk of serotonin syndrome
	Antidepressants, tramadol	↑ drug effect	**Major**, level D	
	Pethidine	↑ drug effect	**Major**, level D	
	Triptans	↑ drug effect	Moderate, level D	

Table continued...

...Table continued

Complementary medicine	Interacting drug	Possible outcome	Severity and level of evidence*	Proposed mechanisms/ comment
	Clopidogrel	↑ bleeding risk	Moderate, level B	Increased conversion to active metabolite
	CYP1A2, CYP2C9, CYP3A4 substrates e.g. imatinib, indinavir, tacrolimus, carbamazepine, phenytoin	↓ drug levels and effect	CYP3A4 = **Major**, level B CYP1A2, CYP2C9 = Moderate, level B	Induces CYP enzymes
	Non-nucleoside reverse transcriptase inhibitors, protease inhibitors	↓ drug levels and effect	**Major**, level B	Induces CYP3A4
	Oral contraceptives	↓ drug levels	**Major**, level B	Risk of breakthrough bleeding/ contraceptive failure
	P-glycoprotein substrates e.g. digoxin, fexofenadine, irinotecan	↓ drug levels and effect	**Major**, level B	Induces intestinal P-glycoprotein
	Simvastatin	↓ drug levels	Moderate, level B	Statin levels reduced by up to 28%
	Warfarin	↓ drug effect	**Major**, level B	Induces CYP1A2, CYP2C9 and CYP3A4
Valerian	Alprazolam	↑ drug levels	**Major**, level B	CYP3A4 inhibitor. Alprazolam increased by 19% in one study.
	CNS depressants	↑ drug effect	**Major**, level D	Pharmacodynamic effect
	CYP3A4 substrates	↑ substrate effect	Moderate, level D	

CYP cytochrome P450

INR international normalised ratio

CNS central nervous system

* Interaction rating adapted from Natural Medicines Comprehensive Database.[11] The level of severity (major, moderate, minor) has been calculated using the evidence and probability of harm. This rating is linked with a generic recommendation for management.

Major Strongly discourage patients from using this combination as a serious adverse outcome could occur. If used, patient should be monitored closely for potential adverse outcomes.

Moderate Use cautiously or avoid combination as a significant adverse outcome could occur. If used, monitor for potential adverse outcomes.

Minor Be aware that there is a chance of an interaction. Advise patients of symptoms that may occur and an action plan to follow.

Level of evidence ratings:

A High-quality randomised controlled trial or meta-analysis

B Non-randomised clinical trial, literature review, clinical cohort or case-control study, historical control or epidemiologic study

C Consensus or expert opinion

D Anecdotal evidence; *in vitro* or animal study or theoretical based on pharmacology

Finding information about complementary medicine interactions

Most complementary medicines are listed (AUST L) medicines, which are not subjected to the same rigorous premarketing safety and efficacy trials as registered (AUST R) medicines. Thus evidence of their interaction potential is often not available. In addition, manufacturers are not obliged to provide a consumer medicine information leaflet with advice or warnings regarding complementary medicine interactions.

Despite the lack of hard data, health professionals still need to make reasonable recommendations to patients about potential interactions. With a view to helping Australians make more informed decisions about using complementary medicines, an independent consortium from Mater Health Services Brisbane, Bond University and University of Queensland, with funding from the National Prescribing Service, evaluated complementary medicines information resources in 2008.[12] Specific criteria were used to identify 52 resources – 26 of these

were shortlisted and assessed for technical quality, content and clinical utility. The quality of drug interaction information was also assessed in the review, specifically whether mechanisms were outlined, degree of severity was stated, and whether the absence of known drug interactions was disclosed.

While many resources (free or subscription) had technical strengths, few had comprehensive interaction coverage. Those with some detail are included for further reading. Two of the highest ranked resources were online subscription databases, both of which contained reasonably comprehensive complementary medicine–drug interaction checkers. These were:

- Natural Standard (www.naturalstandard.com), which provides detailed monographs and brief summaries ('bottom line')
- Natural Medicines Comprehensive Database (www.naturaldatabase.com).

Conclusion

Consumers frequently use complementary medicines in combination with conventional medicines. For this reason, health professionals should always consider the potential for pharmacodynamic and pharmacokinetic interactions between them. High quality evidence is increasingly available for identification and prevention of these interactions.

References

1. Therapeutic Goods Administration. The regulation of complementary medicines in Australia – an overview. April 2006. www.tga.gov.au/cm/cmreg-aust.htm (information last reviewed 2007 Apr 24) [cited 2010 Nov 16]
2. Kotsirilos V. GPs' attitudes toward complementary medicine. Aust Fam Phys 2007;36:270-1.
3. Australian Bureau of Statistics. Australian Social Trends, 2008 Paper 4102.0. www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4102.0Chapter5202008 [cited 2010 Nov 16]
4. Nahin RL, Pecha M, Welmerink DB, Sink K, DeKosky ST, Fitzpatrick AL. Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. J Am Geriatr Soc 2009;57:1197-205.
5. Peng CC, Glassman PA, Trilli LE, Hayes-Hunter J, Good CB. Incidence and severity of potential drug-dietary supplement interactions in primary care patients: an exploratory study of 2 outpatient practices. Arch Intern Med 2004;164:630-6.
6. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008;300:2867-78.
7. Cadieux RJ. Drug interactions in the elderly. How multiple drug use increases risk exponentially. Postgrad Med 1989;86:179-86.
8. Boullata J. Natural health product interactions with medication. Nutr Clin Pract 2005;20:33-51.
9. Dietary supplements – a framework for evaluating safety. Institute of Medicine. Washington, DC: The National Academies Press; 2005. p. 235-46. www.nap.edu/books/0309091101/html [cited 2010 Nov 16]
10. MacGregor JT, Collins JM, Sugiyama Y, Tyson CA, Dean J, Smith L. In vitro human tissue models in risk assessment: report of a consensus-building workshop. Toxicol Sci 2001;59:17-36.
11. Jellin JM, editor. Natural medicines comprehensive database. Therapeutic Research Faculty, Stockton (CA), USA. www.naturaldatabase.com [cited 2010 Nov 16]
12. McGuire TM, Walters JA, Dean AJ, Van Driel M, Del Mar C, Kotsirilos V, et al. Review of the quality of complementary medicines information resources: summary report. Sydney: National Prescribing Service; 2009. www.nps.org.au/__data/assets/pdf_file/0005/69656/CMsInfoSummary.pdf [cited 2010 Nov 16]
13. Bjerrum L, Gonzalez Lopez-Valcarcel B, Petersen G. Risk factors for potential drug interactions in general practice. Eur J Gen Pract 2008;14:23-9.
14. Barnes J, Anderson LA, Phillipson JD. Herbal interactions. Pharm J 2003;270:118-21.

Further reading

Barnes J, Anderson LA, Phillipson JD. Herbal medicines. 3rd ed. London: Pharmaceutical Press; 2007. (book, or as part of MedicinesComplete)

Stockley's Drug Interactions. Baxter K, editor. London: Royal Pharmaceutical Society of Great Britain; 2010. (book, or as part of MedicinesComplete)

Braun L, Cohen M. Herbs and natural supplements: an evidence-based guide. 3rd ed. Sydney: Elsevier Australia; 2010.

The review of natural products. In: Facts & Comparisons. 5th ed. 2008. Wolters Kluwer. www.factsandcomparisons.com/review-of-natural-products-bound.aspx [cited 2010 Nov 16]

Kuhn MA, Winston D. Winston and Kuhn's herbal therapy and supplements, a scientific and traditional approach. 2nd ed. Philadelphia (PA): Wolters Kluwer, Lippincott Williams & Wilkins; 2008.

Therapeutic Goods Administration. Black cohosh (Cimicifuga racemosa): New labelling requirements and consumer information for medicines containing Black cohosh. www.tga.gov.au/cm/0705blkcohosh.htm [cited 2010 Nov 16]

Therapeutic Goods Administration. Kava – safety alerts & advisory statements. www.tga.gov.au/alerts/kava.htm [cited 2010 Nov 16]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 198)

3. St John's wort can decrease phenytoin concentrations via its induction of cytochrome P450 3A4.
4. Ginkgo can increase the bleeding risk when given with warfarin.

Dental notes

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

Drug interactions with complementary medicines

Most dentists are unlikely to ask about the use of complementary medicines when taking their patients' medical histories, however many of these medicines have potentially significant interactions with commonly prescribed drugs. Of particular note is the frequency that many of these medications interact with anticoagulants, particularly warfarin. Many 'blood-thinning' herbal products could result in significant bleeding after not only major oral surgery, but also minor oral procedures. It is therefore advisable that dentists obtain information regarding their patients' use of herbal or complementary medications. However, the routine recommended local measure of haemostatic material in the socket, suture and tranexamic acid as a mouthwash usually controls any bleeding.

Further reading

Abebe W. Herbal supplements may require modifications of dental treatment. Dent Today 2009;28:136-7.

Top 10 drugs

These tables show the top 10 subsidised drugs in 2009–10.

Table 1

Top 10 drugs by DDD/1000 pop/day *†

Constituent drug	PBS/RPBS ‡
1. atorvastatin	80.83
2. irbesartan	33.85
3. perindopril	28.60
4. ramipril	27.35
5. simvastatin	25.55
6. rosuvastatin	25.51
7. paracetamol	24.01
8. candesartan	22.16
9. esomeprazole	21.49
10. aspirin	17.67

DDDs in this table include use in combination products

Table 2

Top 10 drugs by prescription counts †

Drug	PBS/RPBS ‡
1. atorvastatin	11 017 309
2. esomeprazole	6 256 960
3. simvastatin	4 720 865
4. rosuvastatin	4 688 857
5. paracetamol	4 290 327
6. perindopril	3 999 467
7. pantoprazole	3 815 186
8. metformin hydrochloride	3 390 708
9. atenolol	3 140 001
10. irbesartan	3 118 022

Table 3

Top 10 drugs by cost to government †

Drug	Cost to government (A$)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1. atorvastatin	633 711 616	68.94	11 017 309
2. rosuvastatin	291 559 863	25.51	4 688 857
3. ranibizumab	237 199 442	– ¶	113 126
4. clopidogrel	209 904 583	10.39	2 993 979
5. esomeprazole	203 325 839	21.49	6 256 960
6. salmeterol and fluticasone	167 529 715	– §	2 948 869
7. olanzapine	159 202 466	3.00	935 179
8. simvastatin	154 029 119	20.95	4 720 865
9. adalimumab	152 526 189	0.29	85 616
10. rituximab	119 344 969	– ¶	65 225

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† Based on date of supply. Does not include private prescriptions or prescriptions under PBS co-payment.

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

¶ World Health Organization has not allocated a DDD for this drug

§ Combination drugs do not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Database, as at September 2010.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update No. 6; 2010

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

In this issue:

Lamotrigine and serious skin reactions

Summary

Stevens-Johnson syndrome and toxic epidermal necrolysis can develop following lamotrigine administration. Use a lower dose when prescribing lamotrigine with valproate. Advise patients taking lamotrigine to contact their doctor immediately if they experience rash or fever. Discontinue lamotrigine at the first sign of a rash.

Many skin reactions caused by lamotrigine are mild, but serious rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Severe skin reactions occur in 1 in 50–300 children and 1 in 1000 adults taking lamotrigine, and generally appear within the first eight weeks of therapy.[1,2]

As of September 2010, the TGA had received 552 reports of suspected adverse reactions to lamotrigine, 43 (8%) of which were reports of SJS and/or TEN.

SJS and TEN may first present as a prodrome of malaise, fever, headache and cough followed by the sudden appearance of widespread macules, usually on the face, neck and upper trunk, but may appear anywhere on the body. TEN is characterised by widespread bullae which slough over a period of days resulting in large areas of denuded skin.

Although many rashes are mild, there is no way to reliably predict which will develop into serious, potentially life-threatening rashes. Lamotrigine should therefore be discontinued at the first sign of a rash unless the rash is clearly not drug-related.[2]

Many of the cases reported to the TGA involve concomitant use of lamotrigine and valproate, which increases the risk of developing SJS or TEN. Use a lower dose of lamotrigine for patients taking valproate (see the Product Information for details). Avoid high initial doses of lamotrigine and rapid escalation of doses because they also increase the risk of developing a severe skin reaction.

References

1. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2010.
2. Lamictal Product Information. GlaxoSmithKline Australia Pty Ltd. 2010 Feb 3.

Serotonin syndrome: a reminder

Summary

Concomitant use of serotonergic drugs, or use of a single drug in a susceptible patient, can lead to serotonin syndrome which can be life-threatening. The syndrome usually presents as a clinical triad of altered mental status, autonomic dysfunction and neuromuscular excitation, but early signs and symptoms can be mild and easily overlooked. Treatment involves ceasing all serotonergic drugs. Moderate to severe cases usually require hospitalisation and specialist care.

Serotonergic drugs are commonly prescribed in Australia, and carry a risk of serotonin syndrome, especially when used in combination. Any drug that directly or indirectly increases central serotonin neurotransmission at postsynaptic 5-hydroxytryptamine 1A (5-HT1A) and 5-hydroxytryptamine 2A (5-HT2A) can induce serotonin syndrome (see Box 1).

A recent Australian study showed that combinations of drugs with the potential to cause serotonin syndrome are used relatively frequently. In a cohort of over 273 000 elderly war veterans and their dependants, nearly 116 000 (42%) were prescribed at least one serotonergic drug in the period 2000 to 2004. More than 20 000 (8%) had at least one period in which they may have been using two or more serotonergic drugs concomitantly, and over 1800 (0.7%) were dispensed potentially fatal combinations such as a monoamine oxidase inhibitor (MAOI) with a selective serotonin reuptake inhibitor (SSRI), tramadol, or venlafaxine.[1]

Diagnosis

Diagnosis of serotonin syndrome is based on clinical judgement and can be challenging. Mild symptoms can be mistaken for an exacerbation of psychiatric symptoms, and more severe cases for conditions such as neuroleptic malignant syndrome or malignant hyperthermia.

Table 1 lists common clinical features of serotonin syndrome. Generalised hyperreflexia and ankle and ocular clonus suggest a diagnosis of serotonin syndrome because they are not seen in many other conditions.[2,3]

Serotonin syndrome most commonly occurs after a second serotonergic drug is added, or if there has been an inadequate washout interval between changing medicines (see further information, below).[2] It may also be the result of a dose increase or overdose, but may occur even at modest doses in patients with reduced clearance. Dose reduction is recommended in susceptible patients, such as those with hepatic impairment.

Box 1

Drugs that may contribute to serotonin syndrome [2,3]

Antidepressants
SSRIs
MAOIs (reversible and irreversible)
Tricylic antidepressants
SNRIs

CNS stimulants
Amphetamines and derivatives such as MDMA (ecstasy)

Opioids
Tramadol
Pethidine
Dextromethorphan
Fentanyl

Other
Lithium
St John's wort
Tryptophan

SSRI selective serotonin reuptake inhibitor
MAOI monoamine oxidase inhibitor
SNRI selective noradrenaline reuptake inhibitor

Table 1

Clinical features of serotonin syndrome [2–4]

Altered mental status
Confusion, agitation, restlessness, excitement
Autonomic dysfunction
Tachycardia, hypertension, hyperthermia, sweating, mydriasis, flushing, shivering
Neuromuscular excitation
Hyperreflexia, hypertonia, ataxia, tremor, clonus (spontaneous, inducible or ocular)

Treatment

Awareness of the possibility and supportive care are the most important treatments of serotonin syndrome. In most cases symptoms will improve when the serotonergic agents are ceased. Milder cases will usually resolve in 1–3 days. Moderate to severe cases usually require hospitalisation for haemodynamic stabilisation, sedation, temperature control and hydration. Serotonin antagonists such as cyproheptadine and chlorpromazine may be administered, and benzodiazepines may be required to manage agitation.

Further information

Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187:361-5.

For information about switching between antidepressants:

Washout or taper when switching antidepressants. Aust Adv Drug React Bull 2009;28:19.

Therapeutic Guidelines: Psychotropic. Version 6. Melbourne: Therapeutic Guidelines Ltd; 2008.

Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2010.

References

1. Ringland C, Mant A, McGettigan P, Mitchell P, Kelman C, Buckley N, et al. Uncovering the potential risk of serotonin toxicity in Australian veterans using pharmaceutical claims data. Br J Clin Pharmacol 2008;66:682-8.
2. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112-20.
3. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 2007;187:361-5.
4. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter serotonin toxicity criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM 2003;96:635-42.

Drug-induced acute akathisia

Summary

Acute drug-induced akathisia is a relatively common extrapyramidal side effect that can be associated with poor outcomes. Clinicians are reminded to be vigilant to the signs and symptoms of akathisia, particularly in patients taking typical or atypical antipsychotics.

While acute akathisia is seen with typical antipsychotics, it can also occur with atypical antipsychotics, antidepressants (such as selective serotonin reuptake inhibitors (SSRIs)), antiemetics, calcium channel blockers and other medicines.

Akathisia is frequently distressing for patients and in psychiatric settings has been associated with poor medication compliance, agitation, and exacerbations of psychiatric symptoms.[1] Akathisia can be mistaken for anxiety or agitation related to affective or psychotic disorders, which can result in a changes to antipsychotic therapy that worsen the akathisia. A combination of akathisia, depressive symptoms and impulsiveness may contribute to aggressiveness and suicidality in some patients with akathisia.[2]

How common is antipsychotic-induced akathisia?

In the Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE) study, it was estimated that 26–35% of people taking an atypical antipsychotic experienced akathisia each year, compared with 35% taking the typical antipsychotic perphenazine*.[3]

To September 2010 the TGA had received 197 reports of akathisia in which a range of medicines were suspected, including antipsychotics, antidepressants, and antiemetics. An antipsychotic medication was suspected in 62% of reports while more than one drug was implicated in 24% of reports.

Patients with bipolar affective disorder, particularly bipolar depression, may be at a higher risk of developing akathisia with antipsychotics than patients with schizophrenia.[4] Other risk factors include higher antipsychotic doses, high-potency antipsychotics, rapid dose escalation, and psychotropic drug combinations.

Diagnostic issues

The essential underlying feature of akathisia is a subjective feeling of 'inner' restlessness and the drive to move. This can result in significant distress. Objective motor signs of restlessness usually take the form of semipurposeful repetitive movements (e.g. fidgety movements). The subjective component may predominate with there being little or no apparent motor restlessness. The diagnosis of akathisia is a clinical one and can be rapidly assessed (see Box 2). A standardised screening tool, such as the Barnes Akathisia Rating Scale, can aid in diagnosis and monitoring.[5]

Persistent and tardive forms of akathisia can also occur.

Differential diagnoses include restless legs syndrome, drug withdrawal states, tardive dyskinesia, neurological disorders (such as Parkinson's disease, subthalamic lesions), rebound reactions from abrupt withdrawal of psychotropic medication and the activation syndrome sometimes seen with initiation of certain psychotropic drugs (such as partial dopamine agonists, SSRIs, and the serotonin and noradrenaline reuptake inhibitors).

Box 2

Brief clinical assessment for akathisia [1,5]

Ask about:

- feeling of inner restlessness
- desire to walk or pace
- difficulty sitting or standing still
- related distress

Observe for restless movements, such as:

- fidgety movements
- leg swinging while sitting
- rocking from foot to foot
- pacing

Preventing and managing antipsychotic-induced akathisia

To minimise the risk of akathisia, avoid polypharmacy, titrate the antipsychotic dose slowly and use the lowest effective dose.

Antipsychotic-induced akathisia can be managed by stopping unnecessary contributing medicines, reducing the dose or switching to an antipsychotic less likely to cause akathisia.

Some anticholinergic medicines (e.g. benztropine, benzhexol) are registered in Australia for the treatment of drug-induced extrapyramidal symptoms. Lipophilic beta blockers and benzodiazepines are sometimes used in specialist settings to treat antipsychotic-induced akathisia, but are not registered in Australia for this indication.

References

1. Bratti IM, Kane JM, Marder SR. Chronic restlessness with antipsychotics. Am J Psychiatry 2007;164:1648-54.
2. Poyurovsky M. Acute antipsychotic-induced akathisia revisited. Br J Psychiatry 2010;196:89-91.
3. Miller DD, Caroff SN, Davis SM, Rosenheck RA, McEvoy JP, Saltz BL, et al. Extrapyramidal side-effects of antipsychotics in a randomised trial. Br J Psychiatry 2008;193:279-88.
4. Kumar R, Sachdev PS. Akathisia and second-generation antipsychotic drugs. Curr Opin Psychiatry 2009;22:293-9.
5. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672-6.

* not registered in Australia

Unintended pregnancy due to interaction between etonogestrel implant (Implanon) and carbamazepine

Summary

An interaction between hepatic-enzyme-inducing medicines, such as carbamazepine, and etonogestrel implant (Implanon) can lead to contraceptive failure. Depending on the length of co-administration, patients should be instructed to use a barrier method in addition to Implanon, or Implanon should be removed and another non-hormonal contraceptive method used.

Interactions between hormonal contraceptives and other medicines leading to a decreased contraceptive effect are well recognised.[1] For example, carbamazepine can reduce the efficacy of oral and implantable hormonal contraceptives by inducing cytochrome P450 enzymes, which increases clearance of sex hormones.

Implanon is a long-acting progesterone-only contraceptive implant that contains etonogestrel. To August 2010, the TGA had received 32 reports describing contraceptive failure leading to unintended pregnancy due to a suspected interaction between Implanon and carbamazepine.

Women taking hepatic-enzyme-inducing drugs should use a barrier method in addition to Implanon during the time of concomitant drug administration and for 28 days after discontinuation (see Box 3).[2] In women on long-term treatment with hepatic-enzyme-inducing drugs, remove Implanon and recommend a non-hormonal method instead.[2]

References

1. Implanon: interactions and failure of contraception. Aust Adv Drug React Bull 2007;26:4.
2. Implanon Product Information. Schering-Plough Pty Ltd. 2009 Feb 10.

Box 3

Medicines that may decrease the efficacy of Implanon [2]

- Barbiturates
- Griseofulvin
- Nelfinavir *
- Oxcarbazepine
- Phenytoin
- Primidone
- Rifabutin
- Rifampicin
- Ritonavir
- St John's wort
- Topiramate

* not registered in Australia

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

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

ALL suspected reactions to **new medicines**

ALL suspected medicines interactions

Suspected reactions causing

- death
- admission to hospital or prolongation of hospitalisation
- increased investigations or treatment
- birth defects

Reports may be submitted:

- **using the 'blue card'** available from the TGA website (www.tga.gov.au/adr/bluecard.pdf) and in the April, August and December issues of *Australian Prescriber*
- **online** on the TGA website (go to www.tga.gov.au and click on 'report a problem' on the left)
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For further information, please contact the TGA's Office of Product Review on 1800 044 114.

Compression therapy for venous disease

***Mauro Vicaretti**, Senior Lecturer, Vascular and Endovascular Surgery, Sydney Medical School, University of Sydney*

Summary

Compression therapy, by bandaging or stockings, is routine for thromboprophylaxis and for chronic venous disease and its complications, including deep venous thrombosis. The degree of compression is dependent on the condition being treated and underlying patient factors. It is important that a thorough clinical vascular examination with or without non-invasive vascular investigations be performed to rule out significant arterial disease that may contraindicate the use of compression therapy.

Key words: chronic venous disease, compression, deep vein thrombosis, leg ulcer.

(Aust Prescr 2010;33:186–90)

Introduction

Compression therapy has been used to treat chronic venous disease since antiquity, with the earliest recording found in the Corpus Hippocraticum (450–350 BC).[1] Although it remains the cornerstone component in the management of both venous and lymphatic disease, there is no agreement and clarity for prescribing compression therapy.[2]

Compression therapy aims to increase venous and lymphatic return, reducing oedema and venous pressure in the limb, by the application of an external force. Compression can be achieved using bandages, stockings or, in certain circumstances, intermittent pneumatic compression (pressure is applied through a sealed chamber around the limb).

Indications for compression

The recognised indications for compression therapy are:

- tired legs secondary to venous disease
- lower limb oedema
- varicose veins
- skin changes due to venous insufficiency (venous eczema, pigmentation, lipodermatosclerosis, atrophe blanche)
- prevention of deep vein thrombosis
- treatment of deep vein thrombosis or superficial thrombophlebitis
- active or healed venous leg ulcers
- lymphoedema
- prevention of deep vein thrombosis and oedema on long-haul flights (more than four hours).

Assessing the patient

Before compression therapy is commenced, thorough vascular assessment to exclude significant peripheral arterial disease is essential. If pedal pulses are weakened or absent, an ankle-brachial pressure index should be calculated. Divide the ankle systolic pressure of the dorsalis pedis or posterior tibial artery (the greater value taken as the ankle pressure) by the brachial systolic pressure (Figs. 1A–C).

If the patient has arteriosclerosis or diabetes, it is imperative that a great toe pressure index (photoplethysmography) also be performed. This is measured using a photoelectric cell that consists of a light emitting diode and a photosensor that transduces changes in dermal arterial flow. A toe cuff is inflated then deflated (Fig. 1D). A waveform appears when the toe systolic pressure is reached. This pressure is divided by the brachial pressure to give the toe brachial pressure index. A normal toe brachial pressure index is >0.7.

Compression therapy is deemed safe in patients with an ankle-brachial pressure index greater than 0.8. However, reduced compression is advised when the ankle-brachial pressure index is 0.5–0.8. Referral of these patients to a vascular specialist for assessment of arterial disease is also recommended. Compression should be avoided when the ankle-brachial pressure index is less than 0.5, and intermittent pneumatic compression may be considered only after appropriate vascular specialist review (Fig. 2).[3]

Degree of compression

An international standard has been suggested although not accepted by the vascular community. It divides compression levels into mild (<20 mmHg), moderate (≥20–40 mmHg), strong (≥40–60 mmHg) and very strong (>60 mmHg).[4]

A general guide to the amount of compression recommended for various indications is given in Table 1. The sub-bandage pressure (mmHg) required for therapy is determined by patient factors and the underlying disease process. The pressure is directly related to the tension and number of layers applied and indirectly related to the circumference of the limb and bandage width.[5] The application technique and the sub-bandage pressure

Table 1

Guide to recommended compression for various indications

Degree of compression	Indication
<20 mmHg	Prevention of deep vein thrombosis (graduated compression stocking) Mild oedema Tired, aching legs (occupational leg symptoms)
20–30 mmHg	Mild varicose veins Mild to moderate oedema Long-haul flights (>4 hours, high-risk patients for deep vein thrombosis) Varicose veins during and after pregnancy
30–40 mmHg	Venous ulcers (including healed ulcers) Deep vein thrombosis Superficial thrombophlebitis Following venous surgery and sclerotherapy Varicose veins with severe oedema and/or skin changes Post-thrombotic syndrome Mild lymphoedema
>40 mmHg	Severe lymphoedema Severe chronic venous insufficiency

are not only dependent on the type of bandage but also on the skill of the person applying the bandage. Most importantly the final sub-bandage pressure depends on the tension of application.

Irrespective of the method of compression, if there is an ineffective calf muscle pump or limited ankle mobility then the effect of compression therapy is limited. It is likely that variable ankle mobility and calf muscle function may account for much of the variability in the success of compression therapy.[6]

Compression with bandages or stockings

Compression therapy, either by bandages or stockings, can be applied via two principal methods:

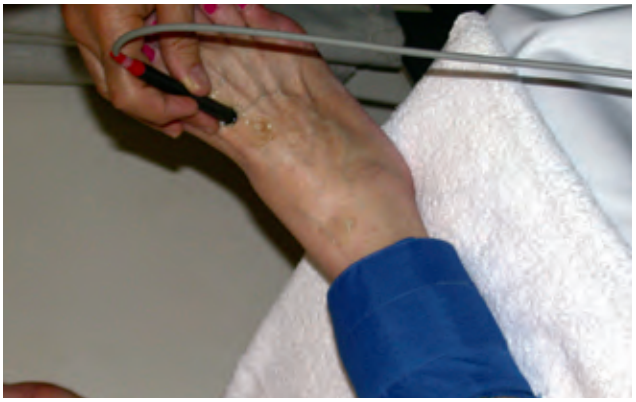
- an elastic system that allows for a high resting pressure and a lower pressure during muscular contraction
- a support system that is relatively rigid and inelastic allowing for a lower pressure at rest and higher pressure during muscular activity.

Both methods may be either single or multilayer.[4]

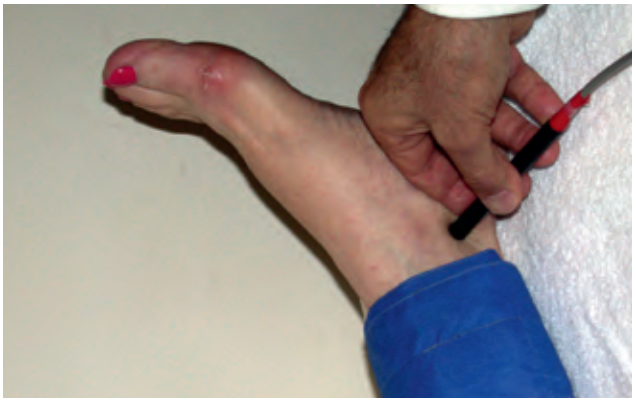
Compression may be achieved with a combination of elastic and inelastic materials which is used in some multilayer systems. It is generally not recommended to apply strong

Fig. 1

Measuring peripheral pulse pressures

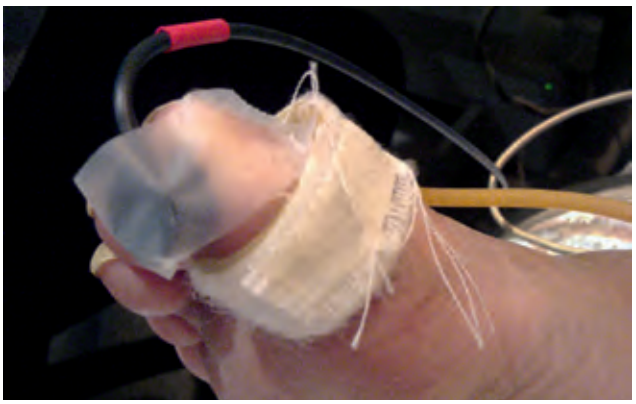


A Measuring dorsalis pedis artery systolic pressure



B Measuring posterior tibial artery systolic pressure

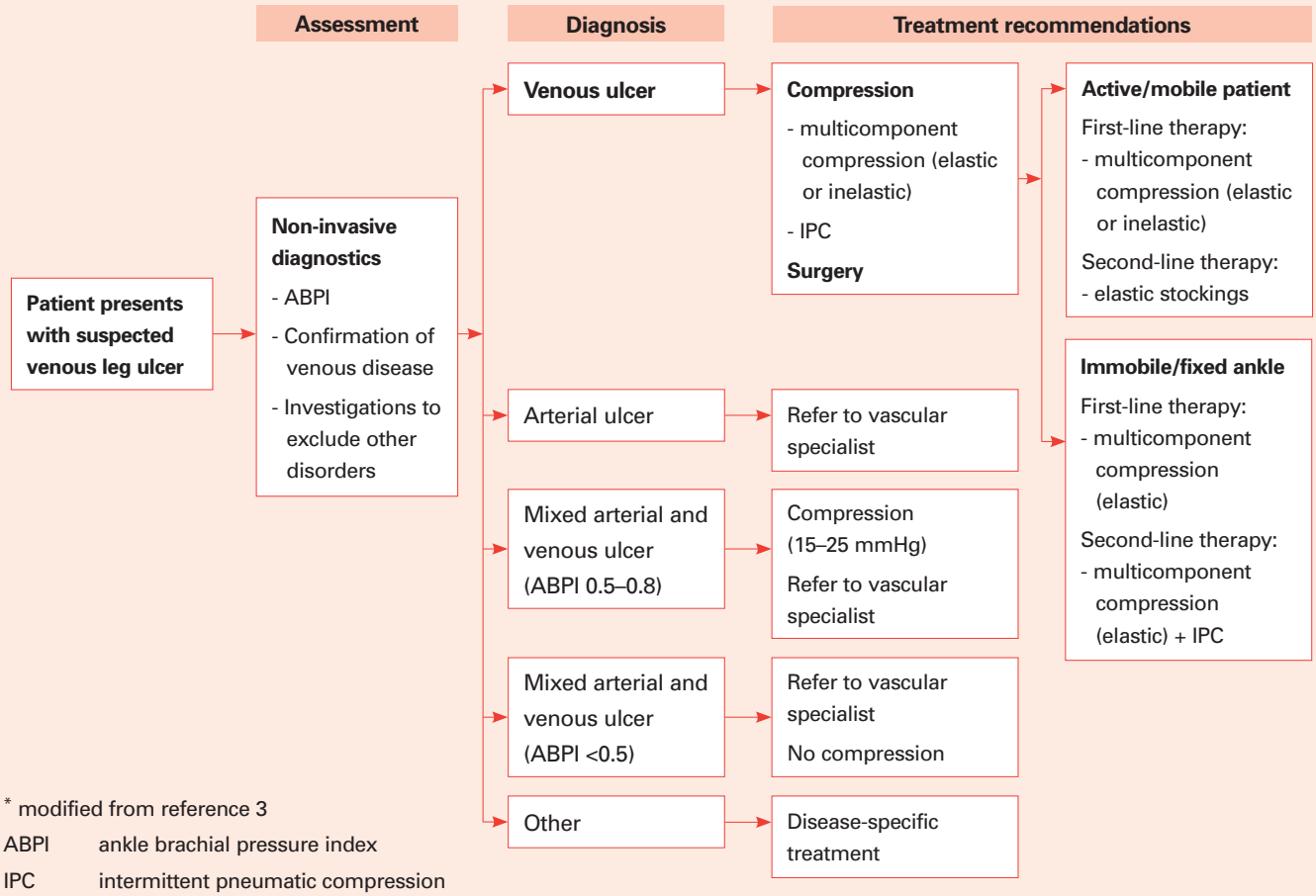
C Measuring brachial artery systolic pressure



D Measuring toe pressure

Fig. 2

Algorithm for the use of compression therapy in venous leg ulcers *



* modified from reference 3

ABPI ankle brachial pressure index

IPC intermittent pneumatic compression

compression with a single elastic bandage because of the risk of skin damage from the pressure. It is preferable to refer to multilayer systems as multicomponent as they generally achieve strong compression independent of the number of layers used.

Bandages

Bandaging can be applied by spiral, continuous or figure of eight methods. There are no data to support one bandaging technique over another.[7] Bandages may be long stretch (extend by more than 100% of original length), short stretch (extend 70–100% beyond original length), or inelastic such as zinc plaster bandages or Velcro devices.[8] Generally, bandaging systems are recommended during the therapy phase of treatment (control of oedema, treatment of venous ulceration, control of lymphoedema). They may also be more practical for those incapable of applying compression stockings or in patients with fragile skin. The disadvantages of compression bandages are the variability of pressure achieved even when applied by experienced professionals, the potential limitations in daily activities such as showering and patient compliance because of discomfort.

Stockings

Medical compression stockings are manufactured from various materials such as silk, cotton, polyester, nylon, natural rubber, polypropylene, or in combination wrapped in elastic. The compression is graduated with maximal compression at the ankle and gradual reduction in compression as the limb circumference increases. They may be panty style, above or below knee, made to measure or available in standard sizes. It is imperative that the appropriate size and compression rating be prescribed for the condition and the patient being treated. There are no direct comparisons on the effectiveness of knee- versus thigh-length stockings, but above-knee stockings are more difficult to apply and have the added risk of creating a tourniquet effect further compromising venous return, especially if the limb being treated is not measured properly. These factors will adversely affect patient compliance. If used daily, compression stockings should be replaced after 3–6 months. Unlike compression bandaging, the pressure generated with stockings is less dependent on the person applying it. Different compression classes are available but pressure profiles are not uniform throughout the world and are measured by non-standardised methods, making comparisons sometimes

difficult. Compression stockings are principally used in the maintenance of limb size and prevention of venous ulceration, oedema and lymphoedema.

Patient compliance with bandages or compression stockings is poorly studied, with non-concordance rates of up to 80% in the 'real world'. This has a negative impact on venous leg ulcer healing and recurrence rates. Patients may not comply with therapy for a number of reasons including lack of patient education, physical factors (pain, difficulty in application), aesthetic and cosmetic factors, cost of therapy, and inappropriate prescribing of therapies by the clinician.[9]

Intermittent pneumatic compression

These devices are airtight chambers (single- or multi-chambered) applied to a limb. They sequentially inflate and deflate, simulating normal circulatory action and venous foot and calf muscle action.[10] This aids venous return, reduces oedema and can even increase arterial flow in the arterially compromised limb.[11] The settings, namely compression pressure up to 80 mmHg, compression time and cycle time, can all be varied. Intermittent pneumatic compression is useful for those not able to tolerate compression bandaging, who have difficulties with controlling limb oedema, have reduced calf muscle function or limited ankle mobility, or who have peripheral arterial disease where other forms of compression are contraindicated.[12] The disadvantages of intermittent pneumatic compression are that it is costly, can be bulky and cumbersome to mobilise with, can be noisy and requires an electrical supply. However, the newer units are more portable with extended rechargeable battery lives.

Reviewing the evidence

Venous ulcers

A recent review of compression for venous leg ulcers concluded that the rate of ulcer healing increased with compression compared with no compression. It also found that multicomponent systems are more effective than single component systems, and those with an elastic bandage are more effective than those with inelastic components.[13] A pressure of 30–40 mmHg at the ankle is recommended for ulcer healing.[14]

Recurrent venous ulcers

Although a review of compression for the prevention of recurrent venous ulcers found there were no trials, circumstantial evidence suggested that people receiving high rather than moderate compression were less likely to develop a new ulcer. It was thus recommended that the strongest compression that the patient would comply with should be prescribed.[15]

Post-thrombotic syndrome

A third to a half of patients with lower limb deep vein thrombosis will develop post-thrombotic sequelae within two years.[16] They may present with minor signs and symptoms such as stasis pigmentation, varicosities, slight pain and swelling, ranging to more major symptoms such as intractable oedema, chronic pain and leg ulcers.[17]

A meta-analysis recommended that all patients with deep vein thrombosis should be prescribed a below-knee graduated elastic compression stocking to reduce post-thrombotic sequelae.[18] Elastic compression stockings should have an ankle pressure of 30–40 mmHg and the compression should be continued for at least two years, and longer in those with post-thrombotic symptoms. In patients with severe oedema, a course of intermittent pneumatic compression is recommended.[19]

Deep vein thrombosis prophylaxis

The role of mechanical devices – graduated compression stockings and intermittent pneumatic compression – is dependent on the risk of venous thromboembolism in the medical or surgical patient. They may be used in combination with drug therapy or alone, especially if drugs are contraindicated because of an unacceptable bleeding risk. These mechanical devices are contraindicated in patients with severe peripheral vascular disease, severe leg deformity and severe peripheral neuropathy.

Evidence supports the use of graduated compression stockings as thromboprophylaxis for abdominal, cardiac, thoracic, vascular, major general or gynaecological surgery, neurosurgery and total hip replacement. Similarly, there is evidence for the use of intermittent pneumatic compression for total hip replacement, hip fracture surgery, total knee replacement, vascular, cardiothoracic surgery, neurosurgery, and for major gynaecological surgery. Graduated compression stockings (ankle pressures of 16–20 mmHg) should be measured for the individual and worn for as long as possible until the patient is fully mobile.[20]

Conclusion

Compression therapy is the mainstay for prevention and treatment of venous and lymphatic system dysfunction. The therapy recommended is dependent on patient factors and the degree of dysfunction. There is a need for a standardised classification of degree of compression to assist in appropriate prescribing.

References

1. Felty CL, Rooke TW. Compression therapy for chronic venous insufficiency. Semin Vasc Surg 2005;18:36-40.
2. Blättler W, Zimmet SE. Compression therapy in venous disease. Phlebology 2008;23:203-5.

3. Marston W, Vowden K. Compression therapy: a guide to safe practice. In: Understanding compression therapy. European Wound Management Association (EWMA) Position Document. London: Medical Education Partnership Ltd; 2003. p. 11-7.
4. Partsch H, Clark M, Mosti G, Steinlechner E, Schuren J, Abel M, et al. Classification of compression bandages: practical aspects. Dermatol Surg 2008;34:600-9.
5. Thomas S. The use of the Laplace equation in the calculation of sub-bandage pressure. EWMA 2003;3:21-3.
6. Bolton L. Compression in venous ulcer management. J Wound Ostomy Continence Nurs 2008;35:40-9.
7. Nicolaides AN, Allegra C, Bergan J, Bradbury A, Cairols M, Carpentier P, et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. Int Angiol 2008;27:1-59.
8. Vin F, Benigni JP, International Union of Phlebology, Bureau de Normalisation des Industries Textiles et de l'Habillement, Agence Nationale d'Accréditation et d'Evaluation en Santé. Compression therapy. International consensus document guidelines according to scientific evidence. Int Angiol 2004;23:317-45.
9. Moffatt C, Kommala D, Dourdin N, Choe Y. Venous leg ulcers: patient concordance with compression therapy and its impact on healing and prevention of recurrence. Int Wound J 2009;6:386-93.
10. Hettrick H. The science of compression therapy for chronic venous insufficiency edema. J Am Col Certif Wound Spec 2009;1:20-4.
11. Partsch B, Partsch H. Calf compression pressure required to achieve venous closure from supine to standing positions. J Vasc Surg 2005;42:734-8.
12. World Union of Wound Healing Societies (WUWHS). Principles of best practice. Compression in venous leg ulcers. A consensus document. London: MEP Ltd; 2008.
13. O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD000265. DOI: 10.1002/14651858.CD000265.pub2.
14. Partsch H, Flour M, Smith P; International Compression Club. Indications for compression therapy in venous and lymphatic disease consensus based on experimental data and scientific evidence. Under the auspices of the IUP. Int Angiol 2008;27:193-219.
15. Nelson EA, Bell-Syer SEM, Cullum NA, Webster J. Compression for preventing recurrence of venous ulcers. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002303. DOI: 10.1002/14651858.CD002303.
16. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. Br J Haematol 2009;145:286-95.
17. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med 2004;164:17-26.
18. Kakkos SK, Daskalopoulou SS, Daskalopoulos ME, Nicolaides AN, Geroulakos G. Review on the value of graduated elastic compression stockings after deep vein thrombosis. Thromb Haemost 2006;96:441-5.
19. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. Chest 2008;133:454S-545S.
20. National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals (2009). Melbourne: NHMRC; 2009.

Conflict of interest: none declared

There is information for consumers with this article at www.australianprescriber.com

Self-test questions

The following statements are either true or false (answers on page 198)

5. Compression therapy is not advised for patients with an ankle-brachial pressure index greater than 0.8.
6. Below-the-knee compression stockings are recommended for at least two years for people with symptoms following deep vein thrombosis.

Collaboration between doctors and pharmacists in the community

***Debbie Rigby**, Consultant Clinical Pharmacist, DR Pharmacy Consulting, Camp Hill, Queensland*

Summary

The role of pharmacists is expanding in primary care. There is evidence that greater collaboration between general practitioners and pharmacists can improve patient care. Medication reviews are an example of how pharmacists can assist general practitioners. Joint training and co-location of practices should encourage increased collaboration between the professions.

Key words: drug utilisation, medication reviews.

(Aust Prescr 2010;33:191–3)

Introduction

Teamwork, communication and collaboration between health professionals are important for the safe and effective delivery of health care.[1] Australia's ageing population and the increasing burden of chronic disease present opportunities and imperatives for health professionals to practise collaboratively.

A literature review by the National Prescribing Service has identified significant problems associated with medication misadventure. Approximately 6% of hospital admissions are associated with adverse drug events and high error rates during transfer of care. Poor communication was the most important common factor contributing to medication errors.[2] Increased interprofessional collaboration between doctors and pharmacists could therefore reduce the considerable medication-related morbidity and mortality.

Role of pharmacists

Pharmacy practice in Australia now involves patient-centred care including counselling, providing drug information, monitoring drug therapy and patient adherence, as well as the supply of medicines. Over the last decade, the role of pharmacists in the community has expanded with the provision of many professional services including medication reviews, diabetes and asthma management programs, and patient medication profiles.

It is in the additional role of managing medication therapy, in collaboration with prescribers, that pharmacists can now make a vital contribution to patient care. To do so, the role of the pharmacist needs to be redefined and reorientated. The traditional relationship between the doctor as prescriber, and pharmacist as dispenser, is no longer appropriate to ensure safety, effectiveness and adherence to therapy. Pharmacists need to pay more attention to patient-centred, outcomes-focused care to optimise the safe and effective use of medicines. Dispensing is, and must remain, a responsibility of the pharmacy profession, but prescribing and dispensing should not be done by the same person. By taking direct responsibility for individual patients' medication-related needs, pharmacists can make a unique contribution to the outcome of medication therapy and to their patients' quality of life.[3]

Collaborative practice

Australian and international studies have shown the benefits pharmacists can make to direct patient care and better medication management.[4,5] In the UK and New Zealand, reviews of medicine use have contributed to professional integration and patient care.[6,7] In Canada, early concerns about collaborative practice have been resolved as general practitioners discovered the benefits of working with pharmacists.[8,9] General practitioners are more likely to accept a pharmacist's recommendations if they have personal contact in case conferences than they are if they are sent written recommendations.[10] General practitioners may be reluctant to use a service led by a pharmacist who they do not personally know.[11]

The TEAMCare coordinated care trial demonstrated that pharmacists and general practitioners can work together in a primary care environment, although a greater degree of trust and collaboration is required.[12] Trust appears to grow over time. When pharmacists are co-located with general practitioners there is a greater opportunity for trust to develop.[13] However, the full effect of pharmacist integration may take longer than one year to perceive clearly.[14]

Studies that have integrated pharmacists into primary care practices have shown improved patient outcomes.[15] Collaborative models have improved the treatment of hypertension.[16] Pharmacists have the potential to optimise drug therapy by identifying medication-therapy problems and recommending solutions.[17] Prescribers are receptive to such recommendations.[18] Pharmacist–patient consultations in relation to medication management within general practitioners' surgeries and in patients' homes have high acceptability to patients.[19]

A role for a pharmacist within a general practice has been proposed to provide multiple risk management strategies

to improve medication safety. The role would focus on interventions to high-risk patient groups and disease states, and would use practice information technology systems to detect potential safety problems.[20]

Interdisciplinary teaching of pharmacotherapeutics provides health professionals with greater insight into their respective roles. This could improve the quality use of medicines and reduce medication errors.[21]

Medication reviews

Medication reviews show the benefits of cooperation. Government remuneration for medication reviews by pharmacists began in 1997 in residential aged care facilities and in 2001 for community patients. Collaborative medication reviews are included in many general practitioner and pharmacist practices, clinical practice guidelines and decision support tools. Several randomised trials have shown improvements in prescribing, and reduced healthcare use and medication costs following medication reviews in patients with hypertension, hyperlipidaemia and diabetes.[22–24]

The evidence supporting the benefits of home medicines reviews continues to expand. They can be effective in delaying the time to next hospitalisation for heart failure,[25] identifying drug-related problems among people receiving treatment for mental illnesses,[26] and assisting in the resolution of medication-related problems.[27] Medication reviews after discharge from hospital have reduced morbidity and mortality in patients with heart failure.[28]

Despite this evidence and considerable support by the Pharmacy Guild and Divisions of General Practice, home medicine reviews are still underused. For example, they are not used enough in the detection and prevention of medication-related problems in cardiovascular disease.[29]

Challenges to collaboration

The dichotomous nature of community pharmacy practice is a critical dilemma for the profession. The role of community pharmacists has been traditionally characterised by dispensing prescription medicines, selling over-the-counter medication and offering healthcare advice. Community pharmacists are often not viewed as a core part of the primary healthcare team. Perceptions around being a retailer and healthcare provider create uncertainty in the minds of the medical profession, funders and consumers. Pharmacy is the only health profession that is reimbursed for its sale of a product rather than provision of a service.

Currently community pharmacists have limited opportunity to see patients in a primary care setting as part of a multidisciplinary team. Direct contact between community pharmacists and general practitioners is often brief and can be perceived as adversarial.

In many cases geographical isolation and separate premises are barriers to the integration of community pharmacists into the primary healthcare team. Electronic health records will potentially overcome some of the barriers with shared access to medication profiles and secure transfer of information. Lack of a private consultation area in a community pharmacy is also a barrier. In addition, the attitudes of doctors towards pharmacists and their contribution to better medication management is another barrier to overcome.[13]

Some medical organisations have been critical of an expanded role for pharmacists in primary health care, opposing pharmacy as the first point of call for treating minor ailments, pharmacist prescribing, disease state management, immunisation and sick notes. However, pharmacists already play a valuable role in triaging minor conditions in the community. People will continue to consult pharmacists for minor health problems as they are a trusted and accessible source of information and advice.

Conclusion

The roles of the doctor and pharmacist are complementary. Good working relationships between all healthcare professionals are essential to the delivery of personalised and effective patient services. All health professions must show greater responsiveness to changing patient needs.

Pharmacists have the skills and knowledge to contribute to the quality use of medicines, to minimise medication misadventure and to help consumers better manage their medicines. Interdisciplinary clinical teaching, communication and relationships are the keys to improving collaboration to achieve optimal medication management. Interprofessional collaboration between general practitioners and pharmacists must continue to evolve to meet the medication management and healthcare needs of the community now and in the future.

References

The full list of references is available online at www.australianprescriber.com with this article in Vol 33 No 6.

1. Institute of Medicine. Creating safety systems in health care organizations. In: Kohn L, Corrigan J, Donaldson M, eds. To err is human: building a safer health system. Washington (DC): National Academy Press; 2001.
12. McDonald P, Rigby D, Roush P, Watts I. GP referral in a group of older community-dwelling people. Aust Pharm 2000;19:107-11.
13. Bradley F, Elvey R, Ashcroft DM, Hassell K, Kendall J, Sibbald B, et al. The challenge of integrating community pharmacists into the primary health care team: a case study of local pharmaceutical services (LPS) pilots and interprofessional collaboration. J Interprof Care 2008;22:387-98.
15. Dolovich L, Kaczorowski J, Howard M, Rodriguez MC, Gaebel K, Haq M, et al; IMPACT team. Cardiovascular outcomes of a pharmaceutical care program integrated into family practices [abstract 21]. Can J Clin Pharmacol 2007;14:e116.
20. Ackerman E, Williams ID, Freeman C. Pharmacists in general practice – a proposed role in the multidisciplinary team. Aust Fam Physician 2010;39:163-4.

25. Roughead EE, Barratt JD, Ramsay E, Pratt N, Ryan P, Peck R, et al. The effectiveness of collaborative medicine reviews in delaying time to next hospitalization for patients with heart failure in the practice setting. Circ Heart Fail 2009;2:424-8.
27. Gilbert AL, Roughead EE, Beilby J, Mott K, Barratt JD. Collaborative medication management services: improving patient care. Med J Aust 2002;177:189-92.
28. Ponniah A, Anderson B, Shakib S, Doecke CJ, Angley M. Pharmacists' role in the post-discharge management of patients with heart failure: a literature review. J Clin Pharm Ther 2007;32:343-52.

Conflict of interest: none declared

New drugs

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

Degarelix

Firmagon (Ferring)

vials containing 80 mg and 120 mg as powder for reconstitution

Approved indication: prostate cancer

Australian Medicines Handbook section 14.3

Androgen deprivation is one approach to the treatment of prostate cancer. This can be achieved by using agonists of gonadotrophin releasing hormone such as goserelin and leuprorelin. Although these drugs cause an initial surge in testosterone, long-term use leads to decreased production.

Degarelix reduces testosterone production by antagonising gonadotrophin releasing hormone. By blocking the pituitary receptors, degarelix cuts testosterone concentrations within a few days, without the surge seen with gonadotrophin releasing hormone agonists.

In a dose-ranging study, 127 patients were randomised to take a starting dose of degarelix followed by monthly maintenance doses. Within three days the testosterone concentration had fallen into the target range in 89% of the men. Low levels were maintained in most of the 87 men who completed the one-year study. Prostate specific antigen was also reduced.[1]

Degarelix has to be given by subcutaneous injection into the abdomen. A depot is thought to form at the injection site so that the drug is slowly released. The half-life of the maintenance dose is estimated to be 28 days. Most of the dose is metabolised by hydrolysis and excreted in the faeces. The dose does not have to be adjusted in patients with mild to moderate renal or hepatic impairment.

Degarelix has been compared with intramuscular leuprorelin in a 12-month study. The 610 men in the study had prostate cancers ranging from localised to metastatic. Those who were randomised to take degarelix were given 240 mg followed by monthly maintenance doses of 80 mg or 160 mg. The desired testosterone concentration was achieved by 97–98% of the degarelix groups and 96% of the leuprorelin group. The reduction in testosterone was more rapid in the degarelix groups. A similar pattern was seen with the reduction in prostate specific antigen.[2]

Adverse effects are common with degarelix. In the comparative study, 40% of patients had injection-site reactions with degarelix. Less than 1% of the leuprorelin group had injection-site reactions. Other adverse effects reported in the trial included flushing, weight gain and altered liver function. Adverse events resulted in approximately 7–9% of the degarelix group and 6% of the leuprorelin group discontinuing treatment.[2] During treatment with degarelix the QTc interval on the ECG can be prolonged and some patients will develop anaemia. Some patients develop antibodies to degarelix although it is yet unclear whether this affects long-term efficacy. Although androgen deprivation has metabolic effects, lipids other than cholesterol, and glucose were not studied. Hypercholesterolaemia occurred in 5% of patients given degarelix.[2]

It appears that an antagonist of gonadotrophin releasing hormone is as effective as an agonist in reducing testosterone concentrations. While at first the reduction is more rapid than with leuprorelin, after about a month there is no significant difference between treatments. Further study will be needed to see the effect of degarelix on survival and whether it has any role in patients who have not responded to a gonadotrophin releasing hormone agonist.

T T T manufacturer provided clinical evaluation

References *†A

1. Gittelman M, Pommerville PJ, Persson BE, Jensen JK, Olesen TK; Degarelix Study Group. A 1-year, open label, randomized phase II dose finding study of degarelix for the treatment of prostate cancer in North America. J Urol 2008;180:1986-92.
2. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008;102:1531-8.

Denosumab

Prolia (Amgen)

vials containing 60 mg/mL solution for injection

Approved indication: osteoporosis

Australian Medicines Handbook section 10.3.3

Denosumab is a humanised monoclonal antibody approved for the treatment of osteoporosis in postmenopausal women. This antibody works by binding RANKL (receptor activator of nuclear factor-κβ ligand) and blocking the interaction with its receptor on the surface of osteoclasts. This inhibits the development and activity of osteoclasts and leads to decreased bone resorption and increased bone density.

Following a subcutaneous dose of denosumab 60 mg, maximum serum concentrations are typically reached one to four weeks later. Denosumab has a half-life of 25–30 days. It is not eliminated via hepatic metabolism and dose adjustment is not needed in patients with renal impairment.

The approval of denosumab for osteoporosis is mainly based on a large phase III randomised trial which enrolled 7868 women aged 60–90 years. These women had to have a bone mineral density T score of less than –2.5 at the lumbar spine or total hip before being randomised to receive subcutaneous denosumab 60 mg or placebo every six months. After three years of treatment, the incidence of new vertebral fractures (measured radiolographically) was significantly lower for denosumab than for placebo (2.3% vs 7.2%). Denosumab also significantly reduced the cumulative incidence of hip fractures (0.7% with denosumab vs 1.2% with placebo) and nonvertebral fractures (6.5% with denosumab vs 8% with placebo). Over the same time period, denosumab was associated with a relative increase in bone mineral density at the lumbar spine (9.2%) and hip (6%) in a subset of 441 women. Markers of bone turnover (serum C-telopeptide) and bone formation (serum procollagen type I N-terminal propeptide) were also decreased in women receiving denosumab.[1] Although the efficacy data from this trial looks promising, a meta-analysis of three randomised controlled trials found that denosumab was not associated with a significant reduction in fracture risk in postmenopausal women.[2]

The efficacy of denosumab in reducing fractures has not been compared to other treatments for osteoporosis. However, a phase III trial looking at bone mineral density compared denosumab (six-month dose) to alendronate (70 mg orally each week) in women with low bone mass (T score ≤ –2.0). After 12 months, bone mineral density of the hip had increased more with denosumab than with alendronate (3.5% vs 2.6%). Although this was statistically significant, the clinical significance of this change is unclear. This increase was associated with a more pronounced decrease in markers for bone turnover in the denosumab group.[3]

In the placebo-controlled trial, eczema and flatulence were more common with denosumab than placebo (3% vs 1.7% and 2.2% vs 1.4%). Cellulitis, a serious adverse event, was also more frequent in women receiving denosumab (12/3886) compared to those receiving placebo (1/3876).[1] This may not be so surprising as RANKL is expressed on immune cells and its inhibition could make people more susceptible to infections. When a larger safety cohort (over 8000 people) was analysed, serious infections were more common with denosumab than placebo (3.4% vs 2.8%) and included abdominal, ear and urinary tract infections as well as cellulitis. Endocarditis, infected arthritis and skin ulcers were also more frequently reported. Malignancies are also a concern with denosumab and cancers were slightly more common with denosumab than with placebo (7.8% vs 7.1%). These risks should be considered when prescribing denosumab and patients should be informed of them.

In the safety cohort, serious pancreatitis occurred more commonly with denosumab than with placebo (9 cases vs 1 case). This proved fatal in two people.

Low osteoclast and osteoblast counts have been observed with denosumab. This could potentially delay healing of fractures. Transient hypocalcaemia can occur with denosumab and is a contraindication to treatment. Calcium and vitamin D supplementation is recommended for all patients. Neutralising antibodies were not found in women who received denosumab.

Denosumab seemed to reduce fractures in postmenopausal women with low bone density in a large placebo-controlled trial. However, because of lack of head-to-head trials it is not known how this efficacy compares with current treatments for osteoporosis. Women may prefer the six-monthly dosing of denosumab but will need to consider its increased risks of infections and malignancies. Postmarketing surveillance for these adverse effects is needed.

T T T manufacturer provided clinical evaluation

References *

1. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756-65.
2. Anastasilakis AD, Toulis KA, Goulis DG, Polyzos SA, Delaroudis S, Giomisi A, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. Horm Metab Res 2009;41:721-9.
3. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res 2009;24:153-61.

Eletriptan hydrochloride

Relpax (Pfizer)

40 mg and 80 mg film-coated tablets

Approved indication: migraine

Australian Medicines Handbook section 16.3.2

Naratriptan, sumatriptan and zolmitriptan are already available for the treatment of migraine. They are now joined by eletriptan, another serotonin (5-HT_1) agonist, which was originally approved for use in Australia in 2000.

Compared with sumatriptan, eletriptan is more lipophilic and has a higher bioavailability. Although at least 80% of the dose is rapidly absorbed, the absolute bioavailability of eletriptan is 50%. The maximum concentration is reached within two hours, but there is a delay if the drug is taken during a migraine attack.

Eletriptan acts on the 5-HT_{1B} receptors which control the constriction of intracranial blood vessels. It also acts on the 5-HT_{1D} and 5-HT_{1F} receptors of the trigeminal nerve.

The half-life of eletriptan is four hours. It is metabolised by the cytochrome P450 system. As CYP3A4 is involved, inhibitors of this enzyme, such as erythromycin or ketoconazole, will increase the plasma concentrations of eletriptan. Eletriptan is therefore contraindicated within 48 hours of treatment with a potent CYP3A4 inhibitor. It is also contraindicated in patients with severe hepatic impairment.

Although eletriptan is mainly eliminated by non-renal clearance, caution is still needed when prescribing for patients with renal impairment. This is because the increase in blood pressure caused by eletriptan is amplified in these patients. The vasoconstrictive effect of eletriptan contraindicates its use in patients with uncontrolled hypertension, coronary heart disease, cerebrovascular disease and peripheral vascular disease. Patients who are at risk of cardiac disease are recommended to have a cardiovascular evaluation before starting treatment with eletriptan. The drug should not be taken at the same time as an ergot alkaloid because of an additive effect on blood pressure.

Hypertension and chest pain are potential adverse effects. More common adverse effects include asthenia, nausea, dizziness and somnolence. The frequency of adverse effects increases with the dose.

The safety of eletriptan in pregnancy is uncertain. Small amounts are excreted in breast milk.

In clinical trials, 54–65% of patients responded within two hours to a dose of 40 mg eletriptan. The headache returned within 24 hours in 23% of patients. A second dose can be taken, if more than two hours have passed since the first dose. There is no point in taking a second dose if there was no response to the first dose.

More patients will respond within two hours to eletriptan than to sumatriptan. In one study 67% of 779 patients taking eletriptan 40 mg improved compared with 59% of 799 patients taking sumatriptan 100 mg. Both drugs were more effective than placebo, because only 26% of the 404 patients in the placebo group responded.[1]

A company-supported meta-analysis has compared eletriptan and sumatriptan. There were 19 randomised placebo-controlled trials of the drugs involving several thousand patients. Compared to sumatriptan 100 mg, a mean of 9.1% more patients will obtain pain relief two hours after taking eletriptan 40 mg.[2]

Another analysis funded by the company compared eletriptan with other members of the class. The numbers of patients who needed to be treated for one to have a 24-hour sustained response were 3.6 for eletriptan 40 mg, 4.9 for sumatriptan 100 mg, 4.5 for zolmitriptan 5 mg and 5.7 for naratriptan 2.5 mg.[3]

T T T manufacturer provided clinical evaluation

References

1. Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. Headache 2003;43:214-22.
2. Mandema JW, Cox E, Alderman J. Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain – results of a model-based meta-analysis that accounts for encapsulation. Cephalalgia 2005;25:715-25.
3. Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. J Manag Care Pharm 2005;11:394-402.

Icatibant

Firazyr (Shire Australia)

pre-filled syringe containing 30 mg/3 mL solution

Approved indication: hereditary angioedema

Australian Medicines Handbook Appendix A

Hereditary angioedema is a rare condition which is characterised by attacks of swelling that can occur anywhere in the body including face, larynx, gut or limbs. It can be painful, particularly with gastrointestinal attacks, and if the larynx is affected asphyxiation and death can occur. Most untreated patients will experience at least one acute attack a month which typically lasts for a few days.

The condition is caused by the absence or dysfunction of the C1 esterase inhibitor. This is thought to lead to increased vascular permeability due to unregulated bradykinin activation.

Icatibant, a synthetic decapeptide, has a similar structure to bradykinin and acts as a competitive antagonist blocking the receptors that bradykinin normally attaches to. Inhibiting bradykinin during an acute attack reduces ongoing inflammatory processes. Treatments for histamine-induced angioedema, such as corticosteroids, antihistamines or adrenaline, have no effect in patients with hereditary angioedema.

In a pilot study of 15 patients with hereditary angioedema, icatibant, given intravenously or subcutaneously, reduced

recovery time from acute attacks compared to historical data from untreated attacks.[1] Based on these findings, randomised controlled trials were conducted.

In a head-to-head trial, subcutaneous icatibant (30 mg) was compared to oral tranexamic acid, another treatment for hereditary angioedema (FAST-2 trial). The median time to onset of symptom relief was shorter for icatibant than tranexamic acid (2 hours vs 12 hours) in the 74 patients.[2]

Icatibant also brought more rapid symptom relief from attacks compared to placebo (2.5 hours vs 4.6 hours) in another study trial of 56 patients (FAST-1 trial). However, this difference was not statistically significant. Not all patients in the controlled trials responded to icatibant immediately – four hours after the start of treatment, 20–33% of patients had not responded.[2]

Icatibant is given as a 3 mL subcutaneous injection in the abdomen so it is not surprising that the most common adverse events are injection-site reactions. These include erythema, swelling, burning, itching and pain. Recurrent angioedema attacks have been reported as serious adverse events with icatibant, but the relationship of these to treatment is unclear.

After injection, icatibant is rapidly absorbed with maximum concentrations being reached after about 30 minutes. It has a terminal half-life of 1–2 hours and its metabolites are mainly excreted in the urine. Cytochrome P450 enzymes are not involved in the metabolism of icatibant and dose adjustments are not needed in renal and hepatic impairment.

Bradykinin has been implicated in the protection of the myocardium during ischaemia. Icatibant could potentially antagonise this protective effect so it should be used with caution in people with acute ischaemic heart disease, unstable angina pectoris or those who have recently had a stroke. Icatibant is not indicated for children.

It is not known if neutralising antibodies develop to icatibant. So far, no signs of increasing hypersensitivity have been observed in patients who have received repeated doses. With adequate training, patients can self-administer icatibant if the doctor thinks it is appropriate. However, if the symptoms are not resolving after two hours, or if the face, lips or pharyngeal area are affected, patients should seek immediate medical help.

Icatibant appears to be an effective treatment for hereditary angioedema, more so than tranexamic acid. It is not known how icatibant will compare to human C1 esterase inhibitor, another recently approved treatment for hereditary angioedema (Aust Prescr 2010;33:89-95).

T T T manufacturer provided clinical evaluation

References †

1. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). J Allergy Clin Immunol 2007;119:1497-503.
2. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010;363:532-41.

Omega-3-acid ethyl esters

Omacor (Abbott)

1000 mg capsules

Approved indications: hypertriglyceridaemia, secondary prevention following myocardial infarction

Australian Medicines Handbook section 6.5.4

A diet rich in fish oils has long been associated with cardiovascular benefits.[1] The components of fish oil include omega-3 polyunsaturated fatty acids. Ethyl esters of two of the acids, docosahexaenoic acid and eicosapentaenoic acid, are contained in the new product. There is currently no complete explanation of how these esters act on triglycerides and the cardiovascular system.

There have been several studies of omega-3-acids and a meta-analysis found that they significantly reduce triglyceride concentrations by 0.3 mmol/L.[2] In an early study, 57 patients with combined hyperlipidaemia were randomised to take the esters or corn oil as an adjunct to diet. After 12 weeks serum triglycerides had reduced by 28% (estimated 1.12 mmol/L absolute change) in the 28 patients who took the esters, but only slightly reduced in those given corn oil. Both treatments significantly reduced total cholesterol, but only slightly increased high density lipoprotein (HDL) cholesterol.[3]

The product has also been studied in 59 patients with serum triglycerides above 2.3 mmol/L who were taking simvastatin. They were randomised to add the omega-3-acid ethyl esters or a placebo for 24 weeks. Serum triglycerides fell from a mean of 4.6 to 3.5 mmol/L with active treatment, but the mean increased with placebo from 3.8 to 3.9 mmol/L. These changes were unrelated to the patients' simvastatin doses.[4]

A larger trial also studied hypertriglyceridaemia in patients taking simvastatin. After dietary advice and taking open-label simvastatin for eight weeks, 256 patients were randomised to add omega-3-ethyl esters or placebo. After a further eight weeks the mean triglyceride concentration had fallen from a baseline value of 282 mg/dL to 202.4 mg/dL (3.19 to 2.29 mmol/L) with the esters and from 286.7 to 275.9 mg/dL (3.24 to 3.12 mmol/L) with placebo. HDL cholesterol increased by 1.8 mg/dL (0.047 mmol/L) with the esters and decreased by 0.7 mg/dL (0.018 mmol/L) with placebo.[5]

The indications for using the esters in hypertriglyceridaemia are restricted. The product is only approved as monotherapy for type IV and V dyslipidaemia. It can be added to therapy of type IIb dislipidaemia if a 'statin' does not produce adequate control.

The main study supporting the use of the esters in secondary prevention after myocardial infarction involved 11 324 patients. They were randomised to take vitamin E, the esters, both or neither. After 3.5 years the relative risk of death, non-fatal myocardial infarction and non-fatal stroke had reduced by 10% in the patients who took the esters compared with those who did not. There was a 26% reduction in the risk of sudden death. Adding vitamin E to the esters did not significantly add to their efficacy.[6] The dose used was 25% of the 4 g recommended for dyslipidaemia so there were only small changes in lipids. This suggests that another mechanism may explain the beneficial effects of the esters after myocardial infarction.

Approximately 4% of patients will stop taking omega-3-acid esters because of adverse effects. Compared with placebo, patients taking them complain more frequently of altered taste and gastrointestinal upsets. Liver function should be monitored in patients with liver dysfunction. Fish oils may prolong the bleeding time, within normal limits, so this effect should be considered if the patient is being anticoagulated or taking aspirin. High doses may increase the concentration of low-density lipoprotein cholesterol. It is uncertain if patients who are allergic to fish have an increased risk of adverse reactions.

Fish oils are an option in the treatment of certain dyslipidaemias. The amount required cannot easily be obtained from the diet. Eating oily fish several times a week may be enough for patients after myocardial infarction. Although the secondary prevention trial showed benefits, they depended on how the data were analysed. In one analysis the esters did not have a significant effect on cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes. A systematic review of omega-3-fatty acids found they did not significantly reduce the risk of death or cardiovascular events.[7] If they are used for secondary prevention, it is important that the patient also takes the standard therapies used after myocardial infarction.

T T manufacturer provided additional useful information

References *

1. Beilin LJ. Fish oils and prevention of cardiovascular disease. Aust Prescr 1987;10:42-55.
2. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis 2006;189:19-30.
3. Grundt H, Nilsen DW, Hetland O, Aarsland T, Baksaas I, Grande T, et al. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. J Intern Med 1995;237:249-59.
4. Durrington PN, Bhatnagar D, Mackness MI, Morgan J, Julier K, Khan MA, et al. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart 2001;85:544-8.
5. Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007;29:1354-67.
6. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447-55.
7. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ 2006;332:752-60.

Pazopanib

Votrient (GlaxoSmithKline)

200 mg and 400 mg tablets

Approved indication: metastatic renal cell carcinoma

Australian Medicines Handbook section 14.2.2

Renal cell tumours tend to be very vascular and are insensitive to chemotherapy (Aust Prescr 2006;29:151–3). Pazopanib, previously GW786034, works by inhibiting the formation of new blood vessels and preventing tumour growth. It inhibits tyrosine kinase by binding to several targets including vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, platelet derived factor receptor-α and -β, and the cytokine receptor c-kit.

There are a number of other angiogenesis inhibitors with a similar action to pazopanib. These include sorafenib, sunitinib and bevacizumab (Aust Prescr 2006;29:9–12 and 2006;29:13–5).

The approval of pazopanib is based on a phase III placebo-controlled trial of 435 patients with locally advanced or metastatic renal cell carcinoma. (About half of these people had previously received cytokine-based treatment such as interferon-alfa or interleukin-2.) Patients took pazopanib until their disease progressed or they died, or they could not tolerate treatment. The median duration of treatment was 7.4 months with pazopanib and 3.8 months with placebo. Oral pazopanib 800 mg (once daily) significantly prolonged progression-free survival compared to placebo (median duration of 9.2 months vs 4.2 months). In terms of tumour response, one patient out of 290 had a complete response to pazopanib and almost a third (87) had a partial response. In the placebo group, there were no complete responses and only 3% of patients (5/145) had a partial response.[1] Overall survival was not statistically different between groups at the time of the analysis.

In the pazopanib group, diarrhoea (52%), hypertension (40%), change in hair colour (38%), nausea (26%), anorexia (22%) and vomiting (21%) were the most common adverse events. More patients dropped out because of adverse events in the

pazopanib group than in the placebo group (14% vs 3%). Arterial thrombotic events (myocardial infarction or ischaemia, cerebrovascular accident) occurred in 3% of patients and 13% had a haemorrhagic event. Just over half of the patients had elevated liver enzymes (serum transaminases, bilirubin) and some of these people had to discontinue treatment. Serious adverse events (grade 3 or 4) to pazopanib were experienced by 40% of patients.[1] Nine of these patients died – reasons included bleeding (4 patients), cardiac event (3), hepatic failure (1) and gastrointestinal perforation (1).

After oral administration, peak concentrations of pazopanib are reached after 2–4 hours. Food increases exposure to this drug so it should be taken on an empty stomach (at least one hour before or two hours after a meal). Tablets should not be crushed as this may affect their rate of absorption. Pazopanib is mainly metabolised by cytochrome P450 3A4, and to a lesser extent by CYP1A2 and CYP2C8. It has a mean half-life of 31 hours and is mainly eliminated in the faeces.

Dose reduction of pazopanib should be considered if strong inhibitors of CYP3A4, such as ketoconazole, ritonavir or clarithromycin, are given concomitantly. Grapefruit juice should be avoided. Inducers of CYP3A4 (rifampicin) may decrease plasma concentrations of pazopanib, and if they cannot be avoided, pazopanib should not be given. Pazopanib use is not recommended with drugs that have a narrow therapeutic window and are metabolised by CYP3A4, CYP1A2 and CYP2C8.

Because of the risk of hepatotoxicity, liver function should be assessed before starting pazopanib and regularly during treatment. Pazopanib may need to be reduced, interrupted or discontinued depending on the results of liver function tests, and specific recommendations are given in the product information. People with moderate hepatic impairment should be given a reduced daily dose and pazopanib is not recommended in patients with severe hepatic impairment.

QT prolongation and torsades de pointes have been reported so pazopanib should be used with caution in patients who have a history of QT prolongation or relevant cardiac disease, or who are taking drugs that prolong the QT interval (see Aust Prescr 2002;25:63–5). In addition, doctors should be cautious when giving pazopanib to patients who have a history or are at increased risk of myocardial infarction, angina, ischaemic stroke and transient ischaemic attack.

As fatal haemorrhage has occurred, pazopanib should not be given to patients with a history of haemoptysis, or cerebral or significant gastrointestinal haemorrhage in the previous six months. Patients with cerebral metastases were excluded from the trials. Fatal gastrointestinal perforation has also been reported and doctors should be vigilant for symptoms.

Hypertension is a common adverse effect of pazopanib and mostly occurs in the first 18 weeks of treatment. Patients should be monitored before starting pazopanib and during treatment. If antihypertensive therapy is not effective, the dose of pazopanib may need to be reduced or discontinued.

Hypothyroidism developed in some patients taking pazopanib so monitoring of thyroid function is recommended. Proteinuria has also occurred – including one serious case – so periodic urinanalysis is advised.

Although pazopanib prolongs median progression-free survival by five months, the risks of adverse effects are considerable. Fatal adverse events – including hepatic toxicity – have occurred with an approximate death rate of 2.2%. Patients should be informed of these risks before deciding whether to start treatment.

It is not known how the efficacy of pazopanib compares to other treatments for renal cell carcinoma but a phase III comparative trial with sunitinib is ongoing.

T manufacturer provided only the product information

Reference *†A

1. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-8.

The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* 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/pmeds/auspar.htm)

Answers to self-test questions

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

Australian Prescriber referees

The Editorial Executive Committee and staff of *Australian Prescriber* would like to thank the following referees who have reviewed our articles over the past five years 2006–10.

Alderman C
Ames D
Atkinson D
Attia J
Babar ZUD
Baigent M
Barraclough B
Bartold PM
Begg E
Beltrame J
Bett N
Boots R
Brennan M
Brieger D
Buckley N
Buring M
Carney S
Carr P
Chapman J
Cheung NW
Collignon P
Cramond T
Cranswick N
Currie B
Davies G
Davies C
Day R
de Costa C
de Malmanche T
d'Emden M
Donohue W
Donovan J
Downing P
Dowsett R
Duggan A
Durrant S
Eris J
Ewald B
Fairley C
Foote AJ
Forge B
Gailer J
Gallus A
Gambrill J
Gatenby P
Gazarian M
Gerschman J
Gibbs H
Gibson P
Gilbert A
Gottlieb T
Graham D
Graham HK
Green M
Greenberg P
Gunasekera H
Habersberger PG
Hall R
Hardman D
Haskett M
Hawley C
Hazell P
Hensley M
Hicks R
Ho K
Hogan C
Hopkins H
Horowitz M
Huang N
Hustig H
Isbister J
Ivanovski S
Jayasinghe R
Jensen B
Joyce D
Juneja S
Katelaris P
Katelaris C
Kellerman G
Kimble FW
Kitching D
Komesaroff P
Kotsirilos V
Kulkarni J
Langguth D
Le Couteur D
Leggett B
Lim A
Lim S
Macintyre P
Mangoni AA
Marks S
Mathew T
McCaughan G
McColl G
McCombe P
McCormack J
McCullough M
McIntyre P
McKensey E
McLachlan A
Michelson J
Mitchell C
Monk D
Morgan T
Moulds R
Nandurkar H
Nash P
Newell C
Nissen L
Nordin C
Norman T
Patterson C
Perkovic V
Phillips P
Phillips K
Pillans P
Pond D
Power D
Proietto J
Reith D
Rigby DA
Roberts-Thompson P
Robinson JS
Robson J
Roughead L
Roush P
Rowe L
Rowe D
Rowell J
Rubinfeld A
Ruffin R
Sansom L
Seale JP
Shakib S
Shann F
Shannon G
Shenfield G
Shield L
Silberberg J
Sinn KW
Spurling L
Stitz R
Stockigt J
Stowasser M
Sturgess A
Sved Williams A
Taylor T
Tebbutt N
Thompson A
Toogood I
Tran H
Tress B
Vajda F
Varigos G
Vasey P
Wainwright D
West M
Wilkinson C
Wilkinson D
Wilson I
Wing LM
Winkel K
Wong R
Young P
Yue D
Zoellner H

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge.

To be sent an e-alert when a new issue is published online, register for e-alerts on the homepage.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. Australian health professionals can subscribe to the paper copy (or update your details) on the homepage, or send in this form.

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* website on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

☐ Change my address

☐ Send me the available back issues

Name: .....

Ref no.: .....
(on the address sheet above name)

Address: .....

.....

.....

Profession: .....
(general practitioner, resident, etc.)

Postal: *Australian Prescriber* Mailing Service
GPO Box 1909
CANBERRA ACT 2601

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

Online: www.australianprescriber.com

See Privacy notice at www.australianprescriber.com/content/privacynotice

Editorial office

For general correspondence such as Letters to the Editor, contact the Editor.

Telephone: (02) 6202 3100 Fax: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600

Email: info@australianprescriber.com

Website: www.australianprescriber.com