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The 'polypill', friend or foe?

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Key words: cardiovascular disease, prevention, population health, risk.

(*Aust Prescr* 2005;28:82-3)

In June 2003 the British Medical Journal (BMJ) published a paper which claimed that taking a daily pill containing six active ingredients would prevent more than 80% of cardiovascular events.¹ The proposed 'polypill' contains aspirin, a 'statin', three blood pressure lowering agents (a thiazide, a beta blocker and an ACE inhibitor) and folic acid. Few papers have provoked such debate and raised tempers so high. One correspondent wrote: 'I have read some rubbish in medical journals in my time, but none as appallingly bad as this'. On the other hand, the Editor of the BMJ said the paper made that issue of the journal possibly the most important in 50 years.

It is generally accepted that patients with previous cardiovascular disease require treatment with antiplatelet, blood pressure lowering and cholesterol lowering therapies.^{2,3} Where the controversy lies is the concept of a fixed dose, and widespread use of the polypill in primary prevention. (The paper suggested that as death from cardiovascular disease increases with age everyone over 55 years old should take the polypill.) Mass medication can be justified from a population perspective when the burden of disease is high, but it is difficult to defend at an individual level in those at low risk.

Another big question is whether benefits of the individual components really would accumulate as suggested. Clinical trials

show that adding one more class of medication does confer additional reduction in risk, but no-one has carried out a study with as many components as in the proposed polypill. Estimates of benefit range from a **relative** reduction in risk around 55% to over 80%, according to the composition of a polypill, with those at highest risk achieving the greatest benefit in **absolute** terms.^{1,3}

Would a one-size-fits-all approach be safe and effective? We don't know if a combination approach would magnify the adverse effects of individual components, although there seems no *a priori* reason to believe it would. It is estimated that the polypill would cause symptoms in 8-15% of people.¹ Some have argued that it would be difficult to tease out which component of the polypill is causing an adverse effect. However, the same is true in any patient who is taking separate drugs at the same time. The components of the polypill and their adverse effects are well known so it should be possible to attribute the cause of an adverse effect.

Critics claim that for many individuals, risk factors would not be adequately controlled by a fixed dose combination. It would however still be possible to tailor treatment with 'top-up' single ingredient tablets where the clinician considered this necessary and different versions of the polypill might be available. Nevertheless, fine-tuning the components of the polypill actually makes little difference to the magnitude of the risk reduction in the whole population. The authors of the BMJ paper argue against intensive monitoring of risk factor levels and subsequent adjustment of treatment, as individual measures of cardiovascular risk discriminate poorly between people who subsequently experience disease events and those who do not.¹

Some people are concerned that a polypill could be too effective, a 'magic bullet' that removes any incentive to adopt healthier lifestyles. This is a weak reason to reject a potentially effective therapy, as is the concern that the polypill would medicalise prevention (iodine in salt and fluoride in the water are perhaps two respectable antecedents). However, it is true that medical interventions can have serious unintended consequences, and the polypill would be to the detriment of personal and population health if it diverted funds and energy from 'upstream' health promotion measures such as smoking cessation, healthy food choices and active environments.

Would people take a polypill? Everyone has a relative or friend who complains of 'rattling' with all their tablets.

In this issue...

Common problems can sometimes be difficult to treat. It is therefore important that the diagnosis is correct. The importance of a thorough history and examination is therefore emphasised in the articles by Gayle Fischer on childhood vulval disease, and by Mark Paine on dealing with dizziness.

While history and examination are essential for diagnosis, laboratory tests are indicated in some cases. Huy Tran tells us about the role of biochemical testing during pregnancy.

The use of antidepressants is increasing. One reason for this rise is the use of the drugs for other indications such as those discussed by Lisa Lampe.

Intuitively the greatest benefit of a polypill is the simplicity of the regimen, resulting in improved adherence and better clinical outcomes, but surprisingly, few clinical trial data are available.⁴ Nevertheless, fixed-dose combinations of four or more medications are being developed for tuberculosis and HIV. For people with cardiovascular disease, in whom the separate ingredients are recommended, only a small minority receive the full combination.⁵ This may result from confusion due to complicated regimens, the sheer inconvenience of managing large numbers of pills, a reluctance to take (or prescribe) multiple medicines, and cost.

A polypill could be very inexpensive because its ideal components are now off-patent. World Health Organization (WHO) analyses show that combination therapy given to people at high absolute risk of cardiovascular disease is more cost-effective than current treatment patterns based on single risk factors (for example treating 'hypertension'). Population approaches like salt reduction in foods are the most cost-effective of all, according to the WHO report.⁶

So why don't we have a polypill already? Innovator companies are reluctant to invest, because profit margins are likely to be thin. Generic manufacturers do not have large research and development budgets. This leaves a gap that government agencies are not ready to fill. What is more, the regulatory hurdles for combinations of three or more ingredients are poorly defined. Despite all this, there are now 'mini' versions of the polypill. For example, last year the United States Food and Drug Administration approved a combination of amlodipine and atorvastatin. The authors of the BMJ paper have a patent on their version of the polypill, though it is difficult to know how defensible this would be, given the components are all generics and the concept is based on published evidence.

At present there seems more heat than light in the polypill

debate. It is time to move on and seek direct evidence from trials. Relatively small studies could investigate whether adherence is improved in patients with established indications for the component medications. An even bigger question is what works best for primary prevention; long-term trials with several thousand participants will be needed to show a reduced event rate. Before casting the polypill as 'friend' or 'foe', we need better information on acceptability, safety and effectiveness.

Acknowledgement: Dr Anthony Rodgers commented on early drafts of this article.

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Dr Rafter is applying for funding for a randomised controlled trial of combination cardiovascular medication.

Transparency – in the eye of the beholder?

Editorial Executive Committee, Australian Prescriber

Key words: drug regulation, drug industry.

(Aust Prescr 2005;28:83-4)

The Editorial Executive Committee of *Australian Prescriber* is concerned about the increasing difficulty of obtaining good information about new drugs. It is not unusual for a drug to be marketed in Australia despite a lack of published peer-reviewed information to support its manufacturer's claims. This is particularly the case for adverse effects and for 'head-to-head' comparisons with older drugs used to treat the same conditions as the new drug. The data (both published and unpublished)

may have been evaluated by drug regulatory authorities so there is a strong argument that their evaluations should be available to health professionals and consumers.

A lot of prominence has recently been given to the need for 'transparency' in the drug regulatory system. For example, there have been calls for an international register of clinical trials so that unfavourable results are not hidden.^{1,2} Greater transparency in the process for subsidising drugs was also an important part of the free trade agreement between Australia and the USA. However, transparency means different things to different people.

The Australian pharmaceutical industry sees increased transparency as the right to scrutinise the deliberations of the Pharmaceutical Benefits Advisory Committee (PBAC). Currently, companies are informed why their drugs are not recommended for subsidy on the Pharmaceutical Benefits Scheme. Increased transparency will give them an opportunity to interact with and scrutinise the basis of the decision.

Disclosing information about the PBAC may improve understanding of its decisions, but the corollary the industry makes is that increased transparency is meaningless unless there is a process for challenging a decision. The call for increased transparency can then be confused with calls for an appeals mechanism.

There are two sides to transparency. Drug companies have been reluctant to make public the information they have submitted to the PBAC, despite the argument that the data for drugs submitted for public subsidy should be open to public scrutiny. The free trade agreement has however enabled the PBAC to release a public summary containing information about how it reaches its decisions. Time will tell how useful this will be to clinicians.

The industry may be concerned about transparency because its dealings with the PBAC include commercially sensitive information about cost-effectiveness. There therefore should be less concern about data which do not include cost information. The data submitted to the Therapeutic Goods Administration (TGA) to support the registration of a drug in Australia deal only with quality, safety and efficacy. This is important information for health professionals and patients, but it is often deemed to be commercial-in-confidence. The TGA does not release any details of its evaluations, unlike the Food and Drug Administration in the USA and the European Medicines Evaluation Agency. We would expect that similar standards of transparency would apply in Australia to help good prescribing. Instead, Australian health professionals and patients often have to rely solely on published information. As the formulations or use of drugs overseas may be different, we cannot always depend on international information.

The withdrawal of rofecoxib in 2004 is a salutary reminder of the difficulty of identifying the adverse effects of a new drug. It is also salutary that the decision to remove rofecoxib from the market was made by the manufacturer, not by the regulatory authorities. The manufacturer was in possession of important safety information that even the regulatory authorities, let alone the prescriber or the public, were not. There have even been suggestions that some companies have tried to limit the dissemination of data for commercial reasons.³

The Editorial Executive Committee supports the call of the International Committee of Medical Journal Editors for a register of clinical trials.¹ The need for a register would be less urgent if the drug regulation process was as transparent as possible. Transparency should not be limited to industry's desire to scrutinise the PBAC. There is a far greater need for the clinical information supporting a new drug to be made public. To explore issues around access to information, National Prescribing Service is holding a seminar in September 2005.*

In future, when *Australian Prescriber* publishes its summary of a new product in the New Drugs section, it will inform readers whether or not the company involved was prepared to provide the journal with the clinical information which was evaluated by the TGA, but has not been made public (see page 103). Companies are gradually accepting the need for transparency and those that are willing to share their information should be recognised.

* Informing Judgements about Medicines. 7–8 September 2005, Sydney. <http://www.nps.org.au/events>

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Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Intravenous potassium chloride

Editor, – Recommendations from the Safety and Quality Council regarding the 'High-risk medication alert: intravenous potassium chloride' (*Aust Prescr* 2005;28:14–16) warrant further comment.

Many elderly and frail patients requiring parenteral

potassium supplementation are readily at risk of volume overload if administered potassium salts in dilute infusions, as illustrated in the article. High dependency and intensive monitoring areas are now being approached to admit and supervise patients merely for the intravenous administration of concentrated potassium salt, or at worst to manage the

consequences of volume overload in those patients given the premixed but dilute solutions on general wards.

Unfortunately staffed beds in such acute areas are usually inconsistently available. The patient is then denied timely potassium replacement therapy or at worst suffers the consequences of delay or volume overload.

Could there not be a more practical approach to developing a safety checking protocol than the recommendations promulgated? It is difficult to believe that any clinically active medical or nursing staff were participants in the recommendations thrust upon and slavishly adopted as a mandate by hospitals nationwide.

P.D. Cameron

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Yvonne Allinson, one of the authors of the article, comments:

Before the release of the first Safety and Quality Council high-risk medication alert, there were examples of innovative and successful risk minimisation projects for intravenous potassium initiated by hospital staff in Australia. The alert sought to raise awareness more broadly and make high level suggestions to assist other facilities, including those without dedicated risk management teams.

The alert asked all facilities to evaluate their current controls against a range of recommended actions. The actions suggested were compiled from the international literature and case studies, Australian adverse incident case studies, positive change management strategies from many hospitals, and consultation with key organisations.*

The alert covered a range of topics where there may be confusion when treating hypokalaemia. These included route of administration, intravenous doses in millimoles only, maximum concentration/rate and the availability of a variety of clinically appropriate premixed dilutions. Importantly it suggested roles for all hospital clinical staff as well as chief executives and key committees.

The alert has stimulated further innovation to make potassium use safer. Facilities need to do their own risk assessment and to develop protocols for safe preparation and use of intravenous potassium. Hospital and facility-based teams are encouraged to draw on local expertise at all levels so that this can be done to safely manage the different clinical risks of individual patients. The alert does not preclude this, rather it hopes to catalyse and encourage such action with follow-up audit, review, evaluation and improvement.

* <http://www.safetyandquality.org.au/index.cfm?page=ACTION#potasalert> [cited 2005 July 4]

Dr Ross Wilson, Chair, National Medication Safety Taskforce, comments:

Dr Cameron highlights a very important issue. That issue is hospitals creating new problems or risks for patients by the way they respond to high level policy recommendations.

The National Medication Safety Taskforce was established in October 2001 to advise the Australian Council for Safety and Quality in Health Care and hence Health Ministers from all jurisdictions, on the reduction of patient harm from the use of medications. It was hoped that the provision on the Council website¹ of case studies from four hospitals from different states would assist with implementation. In addition, the Taskforce hosted a meeting late in 2004 on the practical aspects of implementation of this policy with many key stakeholders, including clinicians. The variation in practice and even knowledge about available potassium products was marked. The other key observation of this group was that reducing the need for intravenous replacement of concentrated potassium should be the subject of major efforts by clinical groups. Recommendations from this meeting are currently being considered, and at the very least could set the scene for better sharing of implementation lessons, as well as agreement to assess the extent of effective reduction of patient risk by local changes in the availability of ampoules of concentrated potassium.

A US survey by the Institute for Safe Medication Practice² found that 96% of clinicians and pharmacists considered that concentrated potassium ampoules were a high-alert medication, with 90% of their organisations having put in place special precautions to reduce the likelihood of error.

If the changes that are made in response to the Australian alert are themselves problematic, then the alert will not have entirely served its purpose. Fortunately, with the passage of time and the sharing of experience this is becoming very much less of an issue. Addressing the clinical management of potassium replacement in hospitals will go a long way to reducing the 'apparent' need for ampoules of concentrated potassium, but will require significant clinical leadership at professional and jurisdictional level.

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Editor, – We read with interest the report 'High-risk medication alert: intravenous potassium chloride' (Aust Prescr 2005;28:14–16) and felt it timely to describe our local experience in a tertiary paediatric hospital.

A small multidisciplinary team (medical, pharmacy and nursing) implemented changes on behalf of the Drug

Utilisation Review Committee over a 10-month period, in accordance with Australian Council for Safety and Quality in Health Care recommendations.¹

An initial intervention took place in March 2004, including the following: removal of excess supplies of potassium-containing ampoules from ward areas, with limited supplies placed in red-labelled boxes in locked medication cupboards. All potassium-containing ampoules were then ordered through the dangerous drugs register, rather than as ward stock. Three preparations of pre-mixed fluids were introduced, each containing 10 mmol KCl per 500 mL (all fluids were 500 mL bags). These changes were audited two and seven months after the intervention.

Adherence to new storage practices for potassium-containing ampoules was noted at the time of the audits in all wards of the hospital. The introduction of pre-mixed intravenous solutions led to a stepwise, substantial reduction in the need for ampoules of concentrated potassium on the wards. As a result, it was possible to remove the ampoules from the majority of general wards of the hospital, without compromising patient care.

The applicability of our project to other institutions presents several challenges. The choice of intravenous solutions varies considerably between the states of Australia, and there is currently no consensus regarding 'ideal' pre-mixed solutions for paediatric patients.

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Acknowledgment: Dr Andrew Numa for review of the manuscript.

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Protection of the public or protection of the pharmaceutical industry?

Editor, –The article 'Should consumers be warned about aspirin, alcohol and gastric bleeding?' (Aust Prescr 2005;28:18–19) contains some peculiar logic. It suggests there is evidence that the risk of upper gastrointestinal bleeding is increased in patients consuming at least three

to five drinks daily. However, it appears that commercial considerations dissuaded the Therapeutic Goods Administration (TGA) from adding an appropriate warning label to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). The primary concern of the TGA should be the health and protection of the public, not the commercial interests of the pharmaceutical industry. Why should marketing considerations enter into the TGA's deliberations at all? Have we not learned from the rofecoxib debacle?

If, as the US Food and Drug Administration (FDA) concluded, there is a problem with moderate–high alcohol intake in combination with the use of aspirin/NSAIDs, then a warning statement for consumers is required. Equally, a similar warning should be required for paracetamol if there is good evidence of an increased risk of hepatotoxicity with alcohol consumption.

It may have been acceptable to conclude that a warning label is not currently warranted because the literature is not clear on alcohol increasing the risk of gastrointestinal bleeding due to aspirin/NSAIDs. However, it is bizarre to conclude that there is a real problem with moderate–high alcohol intake yet not warn consumers because of a need to maintain commercial parity in the analgesic market.

Clinicians are recommended to identify 'at-risk' patients. Would not this be easier if there was an appropriate warning label on analgesic packages, particularly as health professionals may have no knowledge of their patients' consumption of analgesics purchased at supermarkets and other retail outlets?

Gregory Peterson
Professor

Luke Bereznicki
PhD Scholar, National Institute of Clinical Studies
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University of Tasmania
Hobart

Dr J. McEwen, Principal Medical Adviser, Therapeutic Goods Administration, and Dr R. Whiting, Chairman, Medicines Evaluation Committee, comment:

Professor Peterson and Mr Bereznicki express concern that commercial considerations dissuaded the TGA from adding warning labels about alcohol consumption to aspirin and non-steroidal anti-inflammatory drugs. While that implication might be drawn from the article, they can be assured that such was not the case.

The TGA is advised on these matters by the independent Medicines Evaluation Committee (MEC).¹ This committee includes some of Australia's foremost academics and practising clinicians with expertise relevant to over-the-

counter medicines. The most recent consideration of the need for warnings about alcohol intake on analgesic products was in February 2003. At that meeting, the MEC considered a review on non-prescription analgesics.² That review includes at page 36 a speculative question about the reasons for warning statements in the USA, viz: 'Or is there an unstated commercial reason; namely, that if an alcohol warning has to go on paracetamol, it must be placed on aspirin and the NSAIDs so that none of these analgesics is perceived as having a marketing advantage over others in a highly competitive environment?'

It can be stated unequivocally that medical and scientific considerations were the sole determinants of the advice of the MEC to the TGA. Commercial matters were not taken into account.

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Dispensing practices and labelling of drugs

Editor, – Ms McCullagh (Aust Prescr 2005;28:5–7) raises an important point and one that has been brought to the attention of the Pharmacists Board of Queensland. The Board recently undertook disciplinary action against a pharmacist who dispensed a prescription for methotrexate where no label was placed on the bottle holding the tablets. As a direct consequence of the lack of a label, the patient took the wrong dose of methotrexate and was admitted to hospital a few days later with severe toxic manifestations.

The Board subsequently received credible information indicating that the practice of labelling only the exterior packaging when dispensing methotrexate was a not infrequent occurrence. Subsequently it wrote to all Queensland pharmacists highlighting the inherent risks associated with such practice.

The Board supports the comments made by Ms Deans, of the Pharmaceutical Society of Australia. However, it would emphasise that there are very few instances where a pharmacy dispensing label is not able to be securely attached to the container holding the medicine and certainly none where a drug with a narrow therapeutic index is involved, where any patient confusion as to the dose may have dire consequences.

Peter Brand
Chairperson
Pharmacists Board of Queensland
Brisbane

Iron sucrose

Editor, – I read your brief few paragraphs on iron sucrose (Aust Prescr 2005;28:49–51) and felt the need to point out a few things:

- It states in the second paragraph that the sucrose is eliminated in the urine. As prescribing is restricted to patients having dialysis, I doubt very much whether this is true. Most dialysis patients have little or no urine and certainly do not manage to excrete anything worthwhile in their urine.
- The last paragraph regarding safety and efficacy reveals the blindness of Australian authorities. Iron sucrose has been used for over 30 years in more than 50 countries around the world and has a safety record far superior to the currently available iron polymaltose.

The prescribing should be limited to 'dialysis' patients, not just 'haemodialysis' patients – 23% of dialysis patients are peritoneal dialysis patients. Indeed 50+% of patients starting dialysis have commenced erythropoietic agents (legally, and according to guidelines) before they need dialysis. This group will also benefit from iron sucrose so 'chronic renal failure' is a more appropriate indication.

Peter Kerr
Associate Professor
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Clayton, Vic.

Generic prescribing

Editor, – I am concerned about the ongoing push for semi-compulsory generic prescribing. Over many years I have had substantial clinical experience of observing the changed level of health of some patients on changing brands. I have reported some dramatic examples to the Adverse Drug Reactions Advisory Committee (ADRAC).

We should remember that we are NOT just prescribing the active ingredient when we prescribe. There is the issue of varying particle size and varying excipients that may make a difference. For example, I once had a psychotic patient with lactose intolerance and I had to work to identify which brands (or even which strengths of the same brand) of antipsychotics were lactose free. The Pan Pharmaceuticals experience tells us that this is still applicable today and not just a risk from the distant past.

R.J. Taylor
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Vulval disease in childhood

Gayle Fischer, Paediatric Dermatologist, The Children's Hospital at Westmead, and Royal North Shore Hospital, Sydney

Summary

Prepubertal girls with vulvovaginitis usually have a dermatological problem. Dermatitis, psoriasis and lichen sclerosus are the three most common conditions. Poor hygiene is rarely responsible for vulval symptoms and intravaginal foreign bodies are rare. Candidiasis is not seen in the non-oestrogenised vulva and vagina. Infective vulvovaginitis in girls is almost always due to Group A beta-haemolytic streptococci. Sexual abuse is always an issue to be considered in any genital presentation in children, but is rarely a cause of observable vulval disease. Most vulval disease in children can be diagnosed on history and examination alone and no investigation, except a bacterial swab, is required.

Key words: dermatitis, sexual abuse, vulvovaginitis.

(*Aust Prescr* 2005;28:88–90)

Introduction

Girls who present with a vulval rash or itching are often given a prescription for an antifungal cream. This is inappropriate as most cases of vulval itching are caused by an atopic or irritant dermatitis.

Vulval rashes fluctuate in appearance, so the vulva may appear normal. If there have been significant symptoms, review the patient when her symptoms are at their worst. The diagnosis can then usually be made without the need for laboratory tests.

Dermatitis

Girls who suffer from vulval dermatitis are usually atopic and react adversely to common environmental irritants such as soap, bubble bath, using shampoo in the bath, and swimming in chlorinated swimming pools. Healthy children may experience contact dermatitis as a result of contact with faeces most often due to diarrhoea or chronic constipation with soiling. Girls who shower rather than bath may miss washing the vulval area effectively.

Vulval dermatitis presents with vulval itching and a fluctuating rash, often precipitated by contact with irritants. It is exacerbated by excessive washing and the use of antifungal creams.^{1,2} Scratching is a source of embarrassment for the child's parents and attracts unwelcome attention at school. It is common for

girls with vulval itching to wake in a distressed state at night.

Examination is often unremarkable and any rash is poorly defined. Close inspection may reveal some erythema, scale and slight rugosity of the labia majora, and increased erythema and desquamation of the minora. The desquamation may stain the child's underwear and be misinterpreted as a vaginal discharge. If the rash is severe it may extend to the inguinal areas and buttocks. Superinfection with *Staphylococcus aureus* may occur on the skin, but there is no vaginitis and vaginal swabs and urine culture are invariably negative. A greenish discharge in the absence of symptoms or positive bacteriology can be regarded as a normal variant.

Psoriasis

In babies, psoriasis may present for the first time as a persistent nappy rash. In older children the morphology of the rash is an itchy, red, well-demarcated, symmetrical plaque with no scale. The vulva, perineum, perianal area and often the natal cleft may all be involved.^{1,3}

If psoriasis is confined to the vulva, it is difficult to make a definite diagnosis unless there are other diagnostic clues present. A history of cradle cap or problematic nappy rashes as a baby, nail pitting, post auricular or scalp rashes and a family history are all helpful.

Lichen sclerosus

Lichen sclerosus is a rare skin disease with a predilection for the genital area. It is much commoner in females than males. The tendency to develop it is probably genetic as it may be familial and there is an association with autoimmune disease. Although it is usually asymptomatic outside the genital area, it tends to be intensely itchy on the vulva. In children soreness, dysuria, bleeding and chronic constipation may also occur. These children are therefore often investigated for bowel and urinary tract abnormalities and lichen sclerosus can be mistaken for a sign of sexual abuse.^{4,5}

On examination there is a well-demarcated white plaque with a wrinkled surface and scattered telangiectasia which may bleed. The typical distribution is a figure of eight plaque surrounding the vagina and anus, but any pattern on the vulva, perineum or perianal area may be seen. The vagina is not involved. Lichen sclerosus can be complicated by loss of the labia minora and clitoris under scar tissue.

Lichen sclerosus does not always remit at puberty. Although symptoms may settle, silent progression of scarring and atrophy

may occur, and symptom activity may recur later. There is an association (about 2–6%) with squamous cell carcinoma of the vulva in adult life. This cancer has been reported in relatively young women who have had lichen sclerosus since childhood.⁶ Lichen sclerosus should therefore be actively managed and follow-up should ideally be lifelong. Treatment involves the use of a potent topical corticosteroid.⁷

Streptococcal vulvovaginitis

The most common cause of acute vulvovaginitis in prepubertal children is Group A haemolytic streptococcus.⁸ Any case of acute vulvitis in a child should suggest this condition.

The girl presents with a sudden onset of an erythematous, swollen, painful vulva and vagina, with a thin mucoid discharge. There may have been a preceding throat infection with the same organism, or preceding perianal dermatitis.

The infection is easily diagnosed by introital and perianal swabs. It is not necessary to insert the swab right into the vagina, which children usually find traumatic, particularly when the area is tender.

After swabs are taken the child starts either oral penicillin or amoxicillin, or cephalexin if they are allergic to penicillin. The course must run for a full 10 days to prevent recurrence.

Pinworm

Although many children with pinworm infestation are asymptomatic, they can have perianal and vulval itching, particularly at night. An eczematous rash may occur. Pinworm is very well known as a cause of genital itching in children. Many children with vulval disease will already have been treated with mebendazole by their parents or their pharmacist before they see a doctor. If already treated, another cause of itching should be sought.

Fungal infections

Although tinea can present rarely in the genital area in children, candida infections do not occur in healthy children out of nappies. This oestrogen-dependent condition is not seen after infancy in children with normal immune systems.^{1,2,3}

This is an important point, as it is common for children with skin diseases such as dermatitis and psoriasis to be diagnosed as having 'thrush'. Treatment with antifungal creams may cause irritation, particularly if dermatitis is present.

Foreign bodies

Intravaginal foreign bodies are not common. The foreign material is usually fragments of toilet paper or fluff. Small toys are less common.⁹

The child presents with a persistent purulent discharge heavy enough to cause maceration of the vulval skin. Swabs confirm recurrent bacterial infection which responds to courses of

antibiotics but rapidly recurs. The child requires examination under anaesthesia and saline lavage.

Sexual abuse

There is often a greater emotional overlay attached to any condition of the genital area than other parts of the skin. If there is concern about sexual abuse consider referral to a paediatrician or child protection unit. If you are not sure whether the child's problem is a skin condition or a sign of trauma, refer the child to a dermatologist for an opinion before taking any action.

Many parents of children with vulval disease are scared of the possibility of sexual abuse, but few will raise the issue unless prompted. Sexually abused children usually have no physical signs.¹⁰

Management of children with vulval symptoms

Most cases can be diagnosed by the history and examination. A vulval swab may be needed to rule out superinfection or acute streptococcal vaginitis, but a urine culture is not necessary unless there are symptoms of frequency or dysuria. (These can sometimes result from irritation of the opening of the urethra.) Children find vaginal swabs traumatic and a moistened saline swab from the introitus is sufficient if there is vaginal discharge.

Dermatitis

It is important for the parents of children with any form of dermatitis to realise that their child has a chronic problem which may require ongoing daily treatment. Modify the environment to avoid contact with soap, bubble bath and shampoo. It is preferable for girls to bath using a bath oil rather than shower. They should avoid tight lycra clothes and wear cotton underwear. Ask about perfumed products, such as toilet paper and wet wipes, and the use of previous medication both prescribed and over-the-counter.

Chlorinated water is a powerful irritant. Apply vaseline or zinc cream before swimming. Remove the costume and then shower the child before going home.

Incontinence, either enuresis or constipation with overflow, needs to be dealt with. Night nappies should be discarded if possible.

Most cases of vulval dermatitis will respond to 1% hydrocortisone, as long as the environmental changes are also made. Ointment is preferable to creams which may cause stinging. Many parents are very apprehensive about using topical steroids. In practice 1% hydrocortisone is very safe. Pre-empt anxiety with strong reassurance and a warning that the pharmacist, the naturopath and well-meaning relatives may well recommend caution regarding the use of topical steroids. If dermatitis is resistant to treatment with environmental modification and 1% hydrocortisone cream, consider non-compliance, infection and psoriasis.

Psoriasis and lichen sclerosus

When the rash is erythematous but well defined, and particularly when there is perianal involvement, look for other signs of psoriasis and enquire about a family history. A white, well-defined eruption may suggest lichen sclerosus.

A patient with suspected genital psoriasis or lichen sclerosus is best referred to a dermatologist as treatment requires use of a potent topical corticosteroid.

Other conditions

Ask if the child has been treated for possible pinworm infestation. Be aware that a child who complains of persistent symptoms despite repeated normal examination and negative bacteriology may be demonstrating attention-seeking behaviour. If you are unsure, it may be best to refer such patients.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 107)

1. Most cases of vulval dermatitis will respond to 1% hydrocortisone.
2. Candida is the most common cause of vulval itching in prepubertal girls.

Your questions to the PBAC

Adrenaline

I would like to ask the Pharmaceutical Benefits Advisory Committee (PBAC) why repeat prescriptions of the adrenaline auto-injectors, EpiPen and EpiPen Jr, are not available. Anaphylactic risk is a lifelong condition, which will not change much over time. The auto-injectors also have a short half-life so the need to see the doctor for a new prescription every six months just to maintain a supply of a rarely used emergency drug seems inappropriate. A review every couple of years would be reasonable.

Kristen Pearson
Geriatrician
Maroondah Hospital
Ringwood East, Vic.

PBAC response:

Both EpiPen formulations were recommended for listing on the basis of acceptable cost-effectiveness overall, although the estimates of incremental cost-effectiveness were both high

and uncertain. The PBAC therefore recommended a rigorous Pharmaceutical Benefits Scheme (PBS) listing that would prevent use in those instances where cost-effectiveness had not been demonstrated.

To maximise the cost-effective use of the products, the PBAC sought to minimise the number discarded due to the short expiry date by limiting the number of auto-injectors that can be prescribed. Consequently, it recommended that the maximum quantity be limited to one auto-injector for adults and two auto-injectors for patients under 17 years of age, and that no repeats apply.

Data presented to the PBAC indicated that listing with these restrictions would meet the clinical needs of most patients given that on average, the number of auto-injectors required per patient per year (as a replacement for either a used or an expired auto-injector) would be covered by one prescription.

With respect to the short expiry date, I have been advised by the manufacturer that most auto-injectors will expire around 12 months after being dispensed, but it is actively pursuing ways of extending the expiry dates.



Antidepressants: not just for depression

Lisa Lampe, Psychiatrist and Conjoint Lecturer, University of New South Wales at the Clinical Research Unit for Anxiety and Depression, St Vincent's Hospital, Sydney

Summary

Antidepressants can be an effective treatment option for a range of disorders other than depression. These include anxiety disorders, eating disorders and premenstrual dysphoric disorder. The efficacy of antidepressants in these disorders is independent of whether there is a mood disorder. However, there is an important, and sometimes superior, role for psychosocial interventions. Caution is needed in prescribing antidepressants if there is a history of bipolar disorder.

Key words: anxiety disorders, eating disorders, premenstrual dysphoric disorder, cognitive behaviour therapy.

(*Aust Prescr* 2005;28:91–3)

Introduction

In addition to depression, antidepressants may be useful in a range of other disorders. They can be used in the anxiety disorders, and in some eating disorders. The selective serotonin reuptake inhibitors (SSRIs) have been shown to ameliorate the symptoms of premenstrual dysphoric disorder. The tricyclic antidepressants may have a role in the adjunctive management of a range of disorders including chronic pain, headache and enuresis.

Anxiety disorders

Many patients with anxiety disorders do not require drug treatment.

Non-drug treatment

Cognitive behaviour therapy is a highly efficacious treatment for the anxiety disorders. Patients who complete therapy can achieve large reductions in symptom distress and improvements in global functioning. For example, in panic disorder up to 90% of those completing such therapy become panic-free. Exposure-based treatments also have an important role in post-traumatic stress disorder. While pharmacotherapy is associated with high relapse rates following discontinuation, the effect of cognitive behaviour therapy can persist over time. However, some patients are too depressed to participate effectively in cognitive behavioural programs, and comorbid depression is one indicator of poorer outcome. For these patients antidepressant pharmacotherapy may be effective.

Cognitive behaviour therapy can be introduced later as their depression improves.

The question of whether combined cognitive behaviour therapy and antidepressant treatment offers any acute or long-term benefit remains unresolved. In the long term, the inclusion of cognitive behaviour therapy appears to confer some advantage. Hence, current recommendations advise offering cognitive behaviour therapy wherever possible.

Exposure-based programs are the treatment of choice for specific phobias. No drug has established efficacy.

Drug treatment

Although benzodiazepines are effective at reducing the somatic symptoms of anxiety more quickly than antidepressants, they do not result in as great a functional improvement. Antidepressants have an intrinsic anxiolytic action that is not dependent on the presence of comorbid depression or on producing sedation.

Panic

Placebo-controlled trials show that imipramine, clomipramine and the monoamine oxidase inhibitors are efficacious in reducing both the frequency of panic attacks and phobic avoidance.¹ In numerous placebo-controlled trials SSRIs have reduced the frequency and severity of panic attacks, and also improved functioning.

Social anxiety disorder

Monoamine oxidase inhibitors and SSRIs are more effective than placebo, beta blockers and benzodiazepines in the treatment of social anxiety disorder. SSRIs are now considered to be first-line pharmacological treatment and somewhat more than half the patients (or about twice as many as those on placebo) will be much or very much improved.

Obsessive compulsive disorder

In obsessive-compulsive disorder antidepressants only achieve a moderate reduction in symptoms.² Cognitive behaviour therapy has a greater effect. However, approximately 25% of patients refuse this type of treatment and perhaps 25% do not comply with it. In practice, antidepressants and cognitive behaviour therapy are often combined. Only the relatively serotonergic antidepressants, the SSRIs and clomipramine, are effective in treating obsessive compulsive disorder. The benzodiazepines and noradrenergic antidepressants have not been reported to be of benefit.

Generalised anxiety disorder

There are placebo-controlled studies to support the use of certain antidepressants for patients with generalised anxiety disorder. These include imipramine, trazodone (not available in Australia), venlafaxine (a serotonin and noradrenaline reuptake inhibitor) and SSRIs. Importantly, a number of studies have shown antidepressants to be superior to benzodiazepines in relieving the psychic symptoms of anxiety (for example worry, irritability, anxious mood) and equivalent in improving the somatic symptoms. Comorbid depression is particularly common. For these patients early consideration of antidepressant treatment is warranted.

Post-traumatic stress disorder

SSRIs have emerged as first-line pharmacotherapy as they have a more consistent superiority over placebo than monoamine oxidase inhibitors and tricyclics. In addition, several open studies of SSRIs have suggested that they may produce improvements across a broader range of symptoms, including reductions in emotional numbing which is a difficult symptom to treat. As yet, there is little information regarding which patients get the best response, the time course of any response or the optimum dose and duration of treatment.

Using SSRIs in anxiety disorders

SSRIs may have an initial 'activating' effect that can intensify some symptoms of anxiety. It is recommended practice to commence anxious patients on half the minimum tablet strength. The patient remains on this dose for several days to a week until they feel reasonably comfortable; they can then increase to a full tablet. Caution is needed in patients with a history of bipolar disorder as antidepressants can trigger, for example, a manic relapse or rapid cycling.

Many patients will require more than the minimum dose to achieve good control over their symptoms of anxiety and panic. Anxiety disorders differ markedly from depression in the time taken to achieve remission. A recent review reported that after eight weeks of treatment 40–50% of patients have achieved remission, and that this number increases with time.³ There is no evidence to guide the choice of the next antidepressant in the case of non-response or failure to achieve remission.

Eating disorders

Non-drug treatment is the mainstay of management, but antidepressants may have a role in some eating disorders.

Bulimia nervosa

Many antidepressants have been shown in randomised controlled trials to reduce binge eating and purging in patients with bulimia nervosa. Antidepressants also reduce concerns about body weight and shape and reduce symptoms of depression and anxiety.⁴ Tricyclic antidepressants, monoamine oxidase inhibitors, bupropion and SSRIs have all shown efficacy.

There are few controlled follow-up studies. Limited evidence suggests that compared to the treatment of anxiety disorders, there may be better long-term maintenance of gains, providing the initial treatment is continued for long enough (at least six months is recommended). However, it seems that even on continued medication up to one-third of patients may relapse. Open-label studies suggest that changing to a different antidepressant in these cases may produce improvement.⁵

Cognitive behaviour therapy is more effective than antidepressants in bulimia nervosa. The inclusion of cognitive behaviour therapy in a treatment program appears to give some protection against relapse. So far, the evidence is equivocal regarding whether the addition of antidepressants to cognitive behaviour therapy confers any additional benefit in the short term, except to relieve depressive symptoms.⁵

Binge eating disorder

The results of the small number of randomised controlled trials in binge eating disorder suggest that SSRIs may be helpful in reducing binge eating and weight. So far, their long-term effectiveness is unknown.

Anorexia nervosa

In contrast to the bingeing disorders, pharmacotherapy is of no particular value in the treatment of anorexia nervosa. For the severely underweight, nutritional restoration and metabolic stabilisation represent potentially life-saving acute treatment. In the longer term, a holistic, supportive approach is generally recommended, since controlled trials have not shown specific psychotherapy to be superior to non-specific treatment.

Premenstrual dysphoric disorder

Although there has been controversy about the diagnosis, premenstrual dysphoric disorder has been defined as a psychiatric problem. The regular mood disturbance must be differentiated from a primary anxiety or depressive disorder. To establish the diagnosis ask the woman to keep a daily record of her moods and physical symptoms over two successive cycles. Often this in itself will reveal helpful information, for example, identifying exacerbating psychosocial factors that might be amenable to change.

The serotonergic antidepressants (SSRIs and clomipramine), vitamin B₆ (50–100 mg daily), and calcium carbonate (1200 mg daily) given in the luteal phase of the cycle have been shown to be superior to placebo in controlled trials.

SSRIs can reduce the physical and emotional symptoms of premenstrual dysphoric disorder with improvement generally occurring within three cycles. Both continuous dosing (throughout the cycle) and dosing in the luteal phase appear to be effective.⁶ If prescribing the luteal regimen, consider the half-life of the SSRI as discontinuation symptoms may be problematic. Fluoxetine and sertraline are the most studied

SSRIs in premenstrual dysphoric disorder and discontinuation symptoms would not generally be anticipated, especially with fluoxetine given its very long half-life. Doses appear to be within the same range as for the treatment of depression. If a higher dose than the minimum is used and luteal phase dosing is chosen, a short upwards titration is appropriate for SSRIs other than fluoxetine (for example, 50 mg of sertraline for the first three days).⁷

Conclusion

The antidepressants have efficacy in a range of disorders other than depression. In most of these disorders psychological or psychosocial treatments have established efficacy. Antidepressants offer adjunctive treatment for individuals who have a poor response, do not have access to psychological treatments, or who have comorbid depression.

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Dr Lampe is a member of the Wyeth Neuroscience Advisory Board.

Self-test questions

The following statements are either true or false (answers on page 107)

3. Antidepressants are not recommended for the treatment of specific phobias.
4. Antidepressants are less efficacious than cognitive behaviour therapy in the treatment of obsessive compulsive disorder.

Book review

Australian Medicines Handbook 2005

Adelaide: Australian Medicines Handbook Pty Ltd; 2005.

909 pages. Price \$135; students \$99; plus postage. Three-year subscription also available.

Brett Montgomery, General practice registrar, Bunbury, WA

Australian prescribers who are unfamiliar with the Australian Medicines Handbook ought to be pleasantly surprised by its many differences from standard medicines guides.

First, the book's structure is noteworthy. Preceding the individual drug monographs are discussions of drug classes, as well as overviews of clinical topics (e.g. heart failure, angina, hypertension) – thus, it is a sort of hybrid of the MIMS and Therapeutic Guidelines books. In many places, and particularly the antibiotics chapter, its recommendations concur with the latter books.

A difference from MIMS is the handbook's independence from the pharmaceutical industry. It contains no advertising and favours generic drug names in the monographs and index (although brand names and manufacturers are listed).

In general, the monographs present carefully distilled drug information at a level of detail ideal for the busy but critically-minded practitioner. They also include 'practice points' and 'patient counselling' sections, which are refreshingly practical and patient-oriented.

The book has an evidence-based flavour. There are frequent references to evidence from trials, with a consistent mindfulness of clinically relevant (rather than intermediate) end points.

Changes from past editions include monographs on newly marketed drugs and some deletions and altered indications. Also new is a long but easily navigable appendix on drug interactions.

The inclusion of more Pharmaceutical Benefits Scheme (PBS) information would make the AMH more useful. Although the reproduction of the PBS schedule *in toto* in the 1998 edition was unnecessarily detailed, I'd like to see the number of available repeats included next to quantity and PBS listing information. Restricted and authority criteria are usually included, but a reproduction of the PBS lipid-lowering drugs statement would be helpful.

Quibbles aside, the 2005 AMH continues the admirable tradition set by its predecessors. It fills a valuable niche as a source of pithy, accessible, independent and evidence-based prescribing information.



Dealing with dizziness

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Summary

Dizziness is a term used to describe a range of symptoms, but is rarely a sign of a serious disorder. Usually the patient describes vertigo, however they may be referring to a presyncopal sensation or disequilibrium. Clinical evaluation will determine whether the dizziness is vestibular or non-vestibular in origin and then whether the dizziness is peripheral or central in origin. The common causes of vertigo are benign positional vertigo, Ménière's syndrome, vestibular neuritis and migraine.

Key words: Ménière's syndrome, vertigo, vestibular disorders.

(Aust Prescr 2005;28:94-7)

Introduction

Dizziness is a common symptom in general, specialist and hospital practice. Although it is rarely a sign of a life-threatening or serious disorder, it may be incapacitating and result in lost productivity and reduced quality of life. Usually patients complaining of dizziness are referring to vertigo – a sensation of self or environmental motion. Other possibilities exist, for example a light-headed, faint or presyncopal sensation, and sometimes the patient will be actually referring to a gait imbalance. Taking a thorough history will usually clarify the nature of the complaint. Occasionally a slight vestibular disturbance or a slight impairment of cerebral perfusion will produce a rather vague symptom that even the most eloquent of patients will have difficulty describing and will therefore present quite a diagnostic challenge.

Clinical assessment – history

A framework of questions in the clinician's mind will serve as a guide in analysing the patient's complaint.

Is the dizziness of vestibular origin or non-vestibular origin?

Dizziness of vestibular origin (vertigo) is usually provoked or aggravated by movement and improved or relieved by rest (sitting or lying down). Its many causes (Table 1) may be central or peripheral.

The dizziness of benign positional vertigo may be provoked by specific positional manoeuvres while dizziness which is

unaltered between resting and moving about is usually non-vestibular in origin. Dizziness which precedes a blackout or near blackout will usually indicate a syncopal/presyncopal disorder which requires a different approach.

Drugs which can cause dizziness include antihypertensives, anticonvulsants, antidepressants and sedatives. The dizziness occurs either through postural hypotension or direct effects on the central or peripheral vestibular system.

If the patient has vertigo, is it peripheral or central in origin?

Although recurrent isolated vertigo is usually peripheral and benign, this is not always the case. Central vestibular disorders include brainstem lesions and multiple sclerosis. Both the clinician and the patient want to rule out a serious cause, but localising the source of vertigo may be difficult.

The occurrence of associated symptoms may help localise the origin of the vertigo. For example, symptoms such as deafness, tinnitus and aural fullness or pressure might suggest a labyrinthine cause, whereas symptoms such as headache, diplopia, facial/limb paraesthesiae, weakness or clumsiness, dysarthria or dysphagia might suggest a neurological cause.

The temporal profile of vertigo is important in analysing the patient's symptoms. Vertigo lasts less than one minute in benign

Table 1

Causes of vertigo

Common	Less common
Benign paroxysmal positional vertigo	Vertebro-basilar transient ischaemic attack/stroke
Vestibular neuritis/labyrinthitis (acute unilateral peripheral vestibulopathy)	Multiple sclerosis
Ménière's syndrome	Posterior fossa tumours
Migraine	Arnold-Chiari malformation
Psychogenic	Autoimmune inner ear disease
Idiopathic	Perilymph fistula/superior semicircular canal dehiscence
	Invasive middle/inner ear disease (e.g. otomastoiditis, tumours, cholesteatoma)
	Bilateral peripheral vestibulopathy (if asymmetric)

positional vertigo, minutes in transient ischaemic attacks, minutes to hours in migraine and Ménière's syndrome and for more than 24 hours in vestibular neuronitis or posterior circulation stroke.

The patient's medical history may reveal clues to potential causes of vertigo. A history of migraine-like headaches may suggest migraine-associated vertigo, while a recent head injury may suggest a variety of different mechanisms of vertigo. The patient's cardiovascular risk profile may raise the possibility of vascular vertigo.

Is the vertigo spontaneous or provoked?

The circumstances that provoke the symptom of vertigo may provide important clues to possible causes. For example, a change of head position may provoke benign positional vertigo, noise-induced vertigo (Tullio phenomenon) occurs in superior semicircular canal dehiscence, and pressure-induced vertigo (Valsalva, straining, exercise) suggests a perilymph fistula. Hyperventilation may provoke or aggravate psychogenic dizziness, however it may also provoke vertigo from brainstem demyelination or an Arnold-Chiari malformation.

Clinical assessment – examination

A patient with dizziness requires a thorough neurological, otological and cardiovascular examination, including supine and upright blood pressure measurements, particularly if the cause of the dizziness is not apparent from the history. Clearly an abnormality in any of these systems will direct any further investigation and may lead to the diagnosis. For example, an examination for signs of infection may find vesicles near the external auditory canal which would suggest herpes zoster as a cause of dizziness. Frequently, however, many patients with recurrent isolated dizziness will not display any obvious abnormality, particularly if they consult between symptomatic periods.

Nystagmus

If the patient has nystagmus, specific note should be made of the trajectory. Purely vertical or torsional nystagmus suggests a central lesion, whereas a mixed horizontal/torsional nystagmus suggests peripheral vestibular nystagmus.

Note whether the nystagmus is direction changing or direction fixed. Peripheral vestibular nystagmus produces a nystagmus which beats in the same direction regardless of the eye position. Nystagmus which changes direction with different eye positions (for example, beating to the right on right gaze and then beating to the left on left gaze) may indicate a central neurological lesion. The nystagmus of peripheral vestibular disorders tends to be attenuated by visual fixation and so nystagmus may not be detected in the conventional manner in these patients.

Acute severe vestibular insults such as vestibular neuritis may produce nystagmus, which is obvious in the acute phase, but

in many cases this rapidly attenuates over 24–48 hours. The nystagmus may then only be apparent with special techniques. One such technique involves using the ophthalmoscope to observe the nystagmus (movement of the optic disc and retinal vessels) while occluding the other eye to remove visual fixation.

Vestibulo-ocular reflex

Assessment of the vestibulo-ocular reflex is useful in confirming a peripheral origin of vertigo. It is also useful in determining which labyrinth is abnormal. The vestibulo-ocular reflex can be assessed by performing the head-impulse or head-thrust test. This test involves asking the patient to fixate on the examiner's nose. The examiner then rapidly rotates the patient's head to either side (after excluding any significant neck problem). A 10–20° movement is usually sufficient. In healthy people the eyes remain fixed on the examiner's nose regardless of the head position.

In a patient with a labyrinthine lesion, the eyes will move with the head when turned to the side of the lesion and then after a short delay the visual system will trigger a quick corrective eye movement back to the examiner's nose. This quick corrective eye movement is the abnormality sought when undertaking the test. The test will also be abnormal when the head is thrust to either side in a patient with bilateral peripheral vestibular disease, for example gentamicin vestibulotoxicity.

The head-impulse test is also useful in the differential diagnosis of cerebellar infarcts and vestibular neuritis. The test is positive in vestibular neuritis, but negative with a cerebellar infarct.

Visual acuity

Testing the dynamic binocular visual acuity is an additional method of determining whether there is bilateral peripheral vestibular disease. In healthy people the dynamic binocular visual acuity is similar to the static visual acuity. If they can read the 6/6 line on the Snellen chart then they will still be able to read the same line while their head is moving to and fro at approximately two cycles per second. In patients with bilateral peripheral vestibular impairment the visual acuity often drops several lines from the static to dynamic condition, for example from 6/6 to 6/36 or 6/60. Normal dynamic visual acuity does not rule out a unilateral vestibular lesion.

Hallpike manoeuvre

The Hallpike positional manoeuvre is a particularly important part of the clinical examination of the dizzy patient as it can confirm the presence of benign positional vertigo which is one of the commonest causes of vertigo. The manoeuvre should therefore be performed if there is any hint of positional vertigo and in all patients where there is no obvious cause for their symptoms. This is important as benign positional vertigo can be cured with a simple physical positioning manoeuvre and the patient will be very grateful. The manoeuvre is usually simple to

perform. The patient sits upright with the head rotated 30–45° laterally. The patient is then rapidly moved into a supine position on the examination couch with the head hanging over the end of the couch or a pillow placed behind the shoulders. The patient's head is supported either by the examiner or by the couch if a pillow is placed behind the shoulders. The examiner then observes the patient for nystagmus and asks about vertigo. Then the test is repeated with the patient's head turned to the opposite side.

Typically a patient with benign positional vertigo will develop, after a short latency of up to several seconds, a torsional/vertical nystagmus with fast phases directed towards the lower ear accompanied by vertigo. This means the lesion is on the side of the lower ear. Occasionally atypical forms of positional nystagmus will be observed indicating one of the less common variants of peripheral benign positional vertigo or a central form of positional nystagmus.

Further investigation

Some patients presenting with vertigo may require further investigation, however comprehensive audio-vestibular testing does not replace a thorough clinical assessment.

Audio-vestibular investigations may be useful for confirming and characterising suspected vestibular dysfunction. They help to distinguish peripheral from central vestibular disorders, localise the side of peripheral vestibular dysfunction and evaluate the state of adaptation following an insult to the vestibular system. The principal components of quantitative vestibular investigation include electronystagmography, caloric testing and rotational chair testing. An audiogram may be helpful in suggesting a labyrinthine cause of the vertigo, for example the low frequency sensorineural hearing loss seen in Ménière's syndrome.

Imaging of brain, audio-vestibular nerves and labyrinth may be needed, particularly if there are neurological signs or asymmetric sensorineural hearing loss. However, in patients with recurrent isolated vertigo and normal hearing, there is a low yield from imaging studies particularly in regard to cerebellopontine angle tumours or masses.¹

Treatment of vertigo

Basic symptomatic treatment

There is no singularly effective pharmacological treatment to abolish vertigo (see box). Nevertheless a patient can be supported through an acute episode of vertigo with short-term use of vestibular sedatives such as benzodiazepines, antihistamines or prochlorperazine. Antiemetics and bed rest are also useful. The evidence of efficacy of the vestibular sedatives is based on experimental laboratory animal research which shows reduced vestibular neural activity in response to these drugs. Clinical observation of this efficacy is anecdotal and there are no controlled trials.

Drugs used to manage vertigo

Vestibular sedatives

Antihistamines

Diphenhydramine
Promethazine

Benzodiazepines

Diazepam
Lorazepam
Clonazepam

Butyrophenones

Droperidol
Anticholinergics
Hyoscine hydrobromide

Antiemetics

Prochlorperazine
Metoclopramide

Patients with chronic or recurring vertigo are commonly treated with betahistine and/or prochlorperazine although there is no evidence of the drugs' long-term efficacy. These patients will often do well with vestibular adaptation exercises or a formal vestibular rehabilitation program to help manage their symptoms. The drugs prescribed for acute vertigo should be used sparingly as they may impair the vestibular adaptation process.

Selective serotonin reuptake inhibitors such as sertraline may have a role in the management of vertigo, however, they have not been extensively studied.

Treatment of specific causes

The most effective treatment of vertigo is treatment of the specific cause if it can be identified (Table 2).

Benign paroxysmal positional vertigo

Benign positional vertigo can be treated with simple physical manoeuvres, although recurrences are frequent. The particle repositioning manoeuvres, which include the Epley² and Semont manoeuvres, may provide complete symptomatic relief in the majority of patients by moving debris from the semicircular canals to the utricle (see video*). The particle repositioning manoeuvres for benign positional vertigo are 80–90% effective following a single manoeuvre compared to a spontaneous recovery rate of approximately 50% over six weeks. The Brandt-Daroff positional exercises are a possible alternative treatment.

Migraine

Migraine is an important diagnostic consideration in patients presenting with dizziness, whether they have an accompanying headache or not. Although there is no definitive diagnostic test for migraine, there may be a suggestive clinical profile. The response to migraine therapy may strengthen the diagnostic impression.

Table 2

Specific treatment of vertigo

Benign paroxysmal positional vertigo	Otolithic particle repositioning manoeuvre (e.g. Epley ² or Semont manoeuvres), Brandt-Darrof exercises
Vestibular neuritis/labyrinthitis	Bed rest, vestibular sedatives, antiemetics in first 24–72 hours Vestibular adaptation exercises/rehabilitation in recovery phase
Ménière's syndrome	Vestibular sedative, antiemetic for acute episodes Low salt diet +/- diuretic for maintenance treatment Intra-tympanic gentamicin or surgery for severe refractory cases
Migraine	Aspirin, non-steroidal anti-inflammatory drugs, 'triptans', antiemetics in acute episodes Migraine preventive treatment e.g. pizotifen, propranolol, verapamil, amitriptyline, valproate
Psychogenic	Treat associated anxiety/depression/panic disorder Reassurance

Ménière's syndrome

Ménière's syndrome may cause severely disabling and distressing vertigo. Typically patients present with a combination of vertigo, fluctuating low frequency hearing loss/tinnitus and an aural pressure sensation. These symptoms may not necessarily occur simultaneously. Fortunately the majority of patients will respond to conservative medical management including a low salt diet and possibly diuretics. Vestibular sedatives and antiemetics may be useful for prolonged acute attacks. Short-term corticosteroids may be useful in refractory cases with relatively preserved hearing. More aggressive therapies such as intra-tympanic gentamicin and/or surgery are reserved for refractory cases unresponsive to other measures and where there is significant hearing loss. Vestibular rehabilitation therapy may be useful in patients whose symptoms are stable.

Vascular disease

An acute vestibular syndrome resembling vestibular neuritis and recurrent brief isolated vertigo may occur as manifestations of cerebrovascular disease. Increased diagnostic suspicion is required in older patients with associated vascular risk factors. It is, however, unusual for posterior circulation transient ischaemic attacks to manifest as recurrent isolated vertigo for more than a few months.

* See the internet version of this article at www.australianprescriber.com for
 ■ figure showing Epley manoeuvre
 ■ short video (1 min) showing Epley manoeuvre.

See also **Patient Support Organisation: Ménière's Support Group** page 107

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 107)

- There is no effective treatment for benign paroxysmal positional vertigo.
- A bilateral peripheral vestibular impairment can reduce a patient's dynamic visual acuity.



Abnormal laboratory results

Biochemical tests in pregnancy

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Summary

Pregnancy is a normal physiological phenomenon with many biochemical changes ranging from alterations in electrolyte concentrations to more complex changes in cortisol and calcium metabolism. The results of biochemical tests during pregnancy may therefore differ from the normal reference ranges so they may be mistakenly interpreted as abnormal. This can lead to unnecessary and potentially dangerous therapeutic actions. If there is doubt about a result, contact the laboratory to ask if the result reflects the physiological changes that occur during pregnancy. Further investigation and treatment can be recommended if appropriate.

Key words: human chorionic gonadotrophin, thyroid disease.

(*Aust Prescr* 2005;28:98–101)

Introduction

Pregnancy is associated with normal physiological changes that assist the nurturing and survival of the fetus. Biochemical parameters reflect these adaptive changes and are clearly distinct from the non-pregnant state. The woman's renal function, carbohydrate and protein metabolism, and particularly the hormonal pattern are affected. It is critical to appreciate both normal and abnormal changes as laboratory results can influence the management of both mother and child.

Renal function

During pregnancy the serum sodium is about 3–5 mmol/L lower than normal because of an increase in intravascular volume and the resetting of the osmostat. Cardiac output and renal blood flow are also increased. This leads to an increased glomerular filtration rate (GFR) with resultant decrease in concentrations of serum urea, creatinine and uric acid (Table 1).

In most cases, renal function during pregnancy can be adequately assessed by the serum urea and creatinine. If required, the GFR can be calculated using the Cockcroft-Gault or Method of Disease Renal Diet formulae¹, but it is necessary to take into account the pregnant state specifically. The GFR can also be calculated using urinary volume, urinary and serum creatinine. Radioactive studies of urinary excretion are clearly not appropriate.

The renal tubular threshold is also lowered in pregnancy. This results in an increased excretion of uric acid, amino acids and glucose. Urinary testing for glycosuria can therefore be misleading. Similarly, urinary testing to assess metabolic changes should not be used during pregnancy and is best delayed well into the post-partum period. The best practical uses of urine testing during pregnancy are to diagnose pregnancy itself, to detect asymptomatic bacteruria and to warn of imminent pre-eclampsia when protein excretion rises.

Liver function tests

All markers of liver function are generally reduced or low during pregnancy due to the expansion of extracellular fluid. Hence serum albumin, transaminases (AST and ALT) and total bilirubin are low compared with the non-pregnant state. The only exception is serum alkaline phosphatase (ALP) which is elevated due to ALP of placental origin.

Causes of abnormal liver function tests specific to pregnancy include intrahepatic cholestasis of pregnancy, pre-eclampsia, haemolysis-elevated liver enzymes-low platelets (HELLP) and rarely acute fatty liver of pregnancy (Table 1). All of these can cause significant fetal and maternal morbidity and mortality. Newly acquired hepatitis during pregnancy and adverse drug reactions should also be considered when assessing abnormal liver function tests.

Calcium metabolism

During pregnancy, serum total calcium, phosphate and magnesium tend to be low due to the expanded intravascular space. Concentrations of calcium are also affected by the reduced albumin concentration. However, results all remain within the reference range. If there is any doubt regarding the calcium result measure the ionized calcium concentration as it remains unchanged during normal pregnancy despite changes in vascular volume and binding proteins. The concentration of serum parathyroid hormone tends to be 50% lower in pregnancy, despite the increased urinary excretion of calcium as a result of the increased GFR.² Although primary hyperparathyroidism is rare, it remains the commonest cause of hypercalcaemia during pregnancy. However, differentiating it biochemically from familial hypocalciuria hypercalcaemia (which has non-surgical management) is difficult and evaluation at a specialist endocrinology clinic is recommended.

Table 1

Normal reference ranges and their interpretation during pregnancy *

Analytes	Normal (non-pregnant)	Pregnancy	Abnormalities and possible interpretations
Haemoglobin (g/dL)	11.5–16.5	11.0–15.0	} Abnormal results need to be considered in conjunction with the patient's clinical state
White cell count (x 10 ⁶ per mL)	4.0–11.0	Unchanged	
Platelets (x 10 ⁶ per mL)	150–450	Unchanged	
Sodium (mmol/L)	135–145	132–140	} Abnormal results need to be considered in conjunction with the patient's clinical state
Potassium (mmol/L)	3.5–5.5	3.2–4.6	
Urea (mmol/L)	2.5–6.8	1.0–3.8	
			↑ in: dehydration hyperemesis gravidarum late stages of pre-eclampsia renal impairment
Creatinine (mmol/L)	0.06–0.1	0.04–0.08	↑ in: renal impairment late stages of pre-eclampsia
Fasting glucose (mmol/L)	3.0–5.4	3.0–5.0	↑ in: gestational diabetes mellitus (refer to reference 3 for diagnostic criteria)
Total calcium (mmol/L)	2.2–2.60	2.0–2.40	↑ in: primary hyperparathyroidism
Ionized calcium (mmol/L)	1.16–1.30	1.16–1.30	
Magnesium (mmol/L)	0.6–1.0	0.6–0.8	↓ in: vomiting hyperemesis gravidarum
Albumin (g/L)	33–41	24–31	↓ in: malnutrition recurrent vomiting hyperemesis gravidarum
Bilirubin (micromol/L)	3–22	3–14	↑ in: intrahepatic cholestasis of pregnancy HELLP late stages of pre-eclampsia acute fatty liver viral hepatitides
Alanine aminotransferase (U/L)	1–40	1–30	↑ in: intrahepatic cholestasis of pregnancy HELLP late stages of pre-eclampsia acute fatty liver viral hepatitides
Aspartate aminotransferase (U/L)	1–30	1–21	↑ in: intrahepatic cholestasis of pregnancy HELLP late stages of pre-eclampsia acute fatty liver viral hepatitides
Alkaline phosphatase (U/L)	25–100	125–250	↑ in: metabolic bone disorders but placental serum alkaline phosphatase needs to be excluded

Adapted from reference 7

↑ increased concentration

↓ decreased concentration

HELLP Haemolysis-Elevated Liver enzymes-Low Platelets

* Each laboratory, where practicable, should develop its own reference ranges for pregnant women. Care should be exercised in comparing results from different laboratories due to differences in assay methodologies.

Carbohydrate metabolism and gestational diabetes mellitus

The concentration of fasting glucose is reduced during pregnancy because of increased substrate utilisation (Table 1). With the increasing incidence of obesity, there will be an increased prevalence of gestational diabetes and type 2 diabetes developing during pregnancy. It is therefore prudent to be familiar with the diagnostic criteria.³ It is essential to screen for gestational diabetes at 26–28 weeks of gestation so that the correct interpretation can be made. The test is positive if the plasma glucose concentration is 7.8 mmol/L or more one hour after a 50 g glucose load.³

Hormonal changes

Pregnancy causes a remarkable number of hormonal changes that continue to evolve throughout the gestational period. This makes the interpretation of biochemical and hormonal results a challenging task. The changes are a continuation of the luteal phase of the menstrual cycle. Once pregnancy has occurred, concentrations of progesterone and oestrogen continue to rise suppressing the secretion of luteinising hormone and follicle stimulating hormone. However, these changes are non-specific and should not be used to confirm pregnancy.

To confirm pregnancy, serum human chorionic gonadotrophin (HCG) is the test of choice. The concentration of HCG is likely to be elevated by trophoblastic activity as early as day eight after implantation. Concentrations peak at approximately 10 weeks and then decline to plateau out at a lower level.

Thyroid function

Thyroid function tests are not uncommonly ordered during pregnancy and interpreting the results is challenging. Physiologically, the concentration of thyroid stimulating hormone (TSH) normally decreases during the first trimester of pregnancy during which there is maximal cross-stimulation of the TSH receptor by HCG. The TSH concentration then returns

to its pre-pregnancy level in the second trimester and then rises slightly in the third. However, most of the changes still occur within the normal non-pregnant range. Serum free tri- and tetra-iodothyronine concentrations essentially remain unchanged during pregnancy but total concentrations, which include both free and protein-bound fractions, are significantly elevated due to increased circulating binding globulins.⁴ Clinical indicators are usually confounding due to symptoms of pregnancy that can mimic thyrotoxicosis such as nausea, vomiting, heat intolerance, fatigue, anxiety and palpitations. The presence of a goitre, especially in patients with a borderline iodine deficiency, can further confound the diagnosis.

Graves' disease is the commonest cause of true thyrotoxicosis in pregnancy. Where there is prolonged and intractable nausea and vomiting, Graves' disease should be distinguished from hyperemesis gravidarum of pregnancy and transient hyperthyroxinaemia of pregnancy. It is important that they are distinguished from Graves' disease as the prognoses and management are distinctly different (Table 2). Hyperemesis gravidarum and transient hyperthyroxinaemia of pregnancy are often self-limiting and can be treated expectantly with general support and/or beta blockade.⁵ Graves' disease needs to be rigorously controlled in order to optimise both fetal and maternal outcome.⁴

Haematology

In pregnancy, there is a gradual increase in circulating blood volume of up to 1.5 L by the third trimester. As there is a relatively smaller increase in red cell mass there is a decrease in haematocrit and haemoglobin concentrations. The white blood cell and platelet concentrations remain essentially stable throughout (Table 1).⁶

Conclusion

Pregnancy results in many changes to laboratory tests which can be misinterpreted as abnormal. In general, most of the analytes have lower concentrations than in the non-pregnant

Table 2

Distinguishing hyperemesis gravidarum and thyrotoxicosis during pregnancy

	Reference range in pregnancy	Graves' disease	Hyperemesis gravidarum
Thyroid stimulating hormone (IU/L)	0.1–4.0	<0.05	<0.05
Free tetra-iodothyronine (pmol/L)*	10.0–25.0	↑↑↑	↑ to ↑↑
Free tri-iodothyronine (pmol/L)*	3.5–6.0	↑ to ↑↑↑	↑ to ↑↑
Human chorionic gonadotrophin	Normal* for gestational age	Normal* for gestational age	↑↑↑ for gestational age
Thyroid stimulating immunoglobulin	Absent	Present	Absent
Thyroid – myeloperoxidase antibodies	Absent or present in low titre	Absent	Absent or low

↑ increase

* Reference ranges often vary between laboratories

state due to increased intravascular volume while the free active fractions, such as ionized calcium, remain unchanged. It is uncommon for a particular analyte to become elevated and thus this is a useful pointer to recognising abnormal laboratory results during pregnancy. When there are clinically discrepant results, it is prudent to seek further advice from the laboratory.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 107)

7. An increased alkaline phosphatase concentration during pregnancy is abnormal.
8. Glucose excretion is reduced during pregnancy.

Book review

Powerful medicines: the benefits, risks and costs of prescription drugs. Avorn J.

**New York: Alfred A. Knopf; 2004.
448 pages. Price approx. \$57**

John Marley, Pro Vice-Chancellor, Faculty of Health, University of Newcastle, Newcastle, NSW

Reading this book is like sitting on the side of a hill watching a faulty train full of happy passengers hurtling towards inevitable catastrophe and being powerless to stop it happening. In fact it's like watching wreck after wreck take place. In these cases the trains are manufactured by the pharmaceutical industry, the passengers are the trusting patients and the drivers are the prescribers who appear blind to the possibility that there could be any danger ahead. The controllers and signallers are the regulatory authorities who may be in the pay of the train's manufacturers or dominated by politicians.

The book starts with examples of recent drug catastrophes. It lays out how, particularly in the USA, the reach of the pharmaceutical industry is everywhere. The authorities, who should be the guardians of drug safety, are subject to a Congress and Senators in the pay of the industry and they are guided by professional experts who should be objective, but instead are recipients of payments and other inducements to support products and launder data. Although we all suspect this to be the case, the true extent of it is almost beyond comprehension.

The book is a very balanced text as would be expected when the author is one of the world's foremost pharmacoepidemiologists.

It is not all anti-drug or anti-industry, there are sections on benefits as well as risks and costs. There are sections on policy and on how information about drugs is collected and used. There is an excellent discussion about the choices society has to make about how to get the best value from health dollars.

The book has, of course, a heavy focus on the USA. While this may make it of less interest to readers outside that country, there are many similarities with events here that readers will recognise. For example, the infiltration of the research agenda by the pharmaceutical industry as public research funds become more scarce, and the hijacking of postgraduate education in the same way. We also have medical experts, 'key opinion leaders', who have been subtly bought by the industry.

My one criticism is the use of American trade names even though generic names are usually, but inconsistently, given. Although some generic names are cumbersome and not easily recognised, the international reader will not recognise many of the American names.

The book makes complex topics easily comprehensible. What makes the book so readable, beyond the voyeuristic fascination of watching tragedy after tragedy unfold, is Avorn's sharp humour. For example, '... anti-Parkinson drugs are a rough crowd to invite across your blood-brain barrier if you don't have to'.

Jerry Avorn is a world expert and also a brave crusader. Anyone who ever prescribes, dispenses or takes a medication should pause before they do so to read this book. They may make a different choice as a result.

Medicinal mishap

'Statins' and muscle symptoms

Prepared by Treasure M. McGuire and Geraldine M. Moses, Education and Information Unit, Mater Pharmacy Services, Mater Misericordiae Health Services, South Brisbane, Qld

Case

Mr B is 78 years old and has taken simvastatin since 1990. In 1995 he started amiodarone 200 mg daily, but within four months he developed bilateral pain in biceps and thigh muscles. These symptoms have continued on and off since then. He initially brought these symptoms to the attention of his general practitioner, but was reassured that it was not unusual for people in their 70s to suffer from muscle aches and pains.

In late 2003, Mr B's simvastatin dose was doubled to 40 mg twice daily. His symptoms got worse and he tore a muscle while lifting a telephone book. Mr B called the Adverse Medicine Events line (AME Line) querying the possible association between simvastatin and muscle tears, after seeing a similar case reported in a newspaper article about the service. The AME Line classified Mr B as a possible case of statin-induced myopathy due to both a simvastatin-amiodarone drug interaction and a dosage increase. He was provided with published literature on this possible association and advised to return to his doctor for further investigation.

Follow-up revealed that Mr B had an elevated creatine kinase. His dose of simvastatin was subsequently reduced to 10 mg twice daily and ezetimibe was added to his regimen. The patient described gradual improvement of his symptoms over the following eight weeks.

Comment

Mr B's case shows the importance of having a mechanism for consumers to report possible adverse events. Consumer-derived adverse drug reaction reports complement reports from health professionals¹, and may partly address under-reporting of adverse drug reactions by health professionals.²

The AME Line, operated by pharmacists of Mater Health Services Brisbane, was established in October 2003 as a project of the Australian Council for Safety and Quality in Health Care to examine the contribution of consumers to adverse medicine event reporting (both adverse drug reactions and errors related to medicines). Over 2400 consumer reports have been received by the service, with approximately 50% involving symptoms that were ultimately judged likely to be medicine-related. Approximately 20% of the total met the Adverse Drug Reactions Advisory Committee (ADRAC) criteria for reporting, and almost 10% involved medication errors.

Mr B was one of 174 people who called the AME Line with

concerns about 'statin'-induced symptoms, in response to the newspaper article. These cases were associated with:

- increased age
- recent commencement of a statin
- dose increase of the statin
- drug interactions that elevate the statin level, e.g. co-administration of cytochrome P450 (CYP) 3A4 inhibitors such as amiodarone with a statin metabolised by CYP3A4 such as atorvastatin and simvastatin
- pre-existing condition(s) which contribute to an elevated statin plasma concentration, e.g. decreased renal function, dehydration, liver dysfunction or hypothyroidism.

Detailed analyses of these cases, in conjunction with ADRAC, led to the development of a checklist to assist practitioners to determine possible statin-induced musculoskeletal adverse effects (see box).

Conclusion

The AME Line provides an opportunity for Australian consumers to contribute to post-marketing pharmacovigilance. Muscle symptoms with statins may be more common than health professionals suspect.

References

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Adverse Medicine Events Line 1300 134 237
(Mon–Fri 9am–6pm EST)

Checklist for statin-induced muscle symptoms

Does the patient experience:

- muscle aches, tenderness, soreness, weakness or pain, usually present in proximal muscles (e.g. trunk)
- bilateral symptoms
- decreased muscle strength (not just feeling tired)
- difficulty in:
 - getting up from a chair
 - holding arms above the head
 - performing usual tasks (generalised difficulty)

Are any of the following concentrations increased:

- creatine kinase
- erythrocyte sedimentation rate
- C-reactive protein

Two-way transparency

For several years there have been complaints about the transparency of the Australian drug regulatory system. Pharmaceutical companies complain about the transparency of decisions to approve or reject a product for marketing or subsidy, while clinicians complain that they cannot access the data used to make those decisions.

The Pharmaceutical Benefits Advisory Committee has been working with the pharmaceutical industry to address some of these criticisms. Greater transparency of the operation of the Pharmaceutical Benefits Scheme (PBS) was also a key feature of the free trade agreement between Australia and the USA.

While the pharmaceutical industry has achieved some of its goals, much of the clinical data it provides to government remains secret. The Editorial Executive Committee believes that clinical information which could be used to help patients should not be kept as 'commercial-in-confidence'.^{1,2}

In view of the pharmaceutical industry's interest in greater transparency, the Editorial Executive Committee has been

inviting companies to supply the information that supported the approval of their products in Australia. This information can then be used in the preparation of the New Drugs section of *Australian Prescriber* and enhances the evidence base for these comments.

While there has been a range of responses (Table 1), the Editorial Executive Committee is pleased that some companies are willing to provide information for independent review. Companies have also been supplying information to assist the National Prescribing Service in preparing its RADAR review of new listings on the PBS. We hope this is the beginning of a trend which will lead to increased transparency in drug regulation.

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Table 1

T-Score: Pharmaceutical company responses to requests for clinical evaluation data July 2003 – June 2005

Company	Drug	Company	Drug
Manufacturer provided all requested information T T T		Manufacturer declined to supply data X	
Abbott	adalimumab	GlaxoSmithKline	ropinirole
Bristol-Myers Squibb	atazanavir	Janssen Cilag	norelgestromin and ethinyloestradiol
Ferring	carbetocin	Novo Nordisk	insulin detemir
Gilead Sciences	adefovir dipivoxil	Schering	disodium gadoxetate
Lundbeck	escitalopram	Manufacturer did not respond to request X	
Pfizer	eplerenone	Amgen	cinacalcet
Roche	enfuvirtide	ANSTO Radiopharmaceuticals	iobenguane [¹²³ I] sulphate
Specialites Septodont	articaïne	Aventis Pasteur	inactivated cholera vaccine
Manufacturer provided some data T T		Aventis Pharma	insulin glulisine
CSL Ltd	bivalirudin	Baxter Healthcare	iron sucrose
Eli Lilly	atomoxetine	Baxter Healthcare	human protein C (plasma derived)
Eli Lilly	pemetrexed	Baxter Healthcare	amotosalen
Genzyme	agalsidase beta	Biogen	alefacept
Laboratoires Fournier	fenofibrate	Bracco	gadobenate dimeglumine
Merck Sharp & Dohme	aprepitant	Douglas	poractant alfa
Novartis	ketotifen hydrogen fumarate	Gilead Sciences	emtricitabine
Schering	iloprost	GlaxoSmithKline	fosamprenavir
Servier	strontium ranelate	Novartis	everolimus
Manufacturer had no objection to providing data but did not actually provide it T		Novartis	darifenacin hydrobromide
AstraZeneca	rosuvastatin	Pfizer	tolterodine tartrate
Genzyme	laronidase-rch	Solvay	moxonidine
Novartis	lumiracoxib		
Orphan	treprostinil		
Pharmion	thalidomide		
Pfizer	pregabalin		
Serono	efalizumab		

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been 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.

Balsalazide sodium

Colazide (Pharmatel)

750 mg capsules

Approved indication: ulcerative colitis

Australian Medicines Handbook section 12.6.2

Mesalazine is an aminosalicic acid derivative which has been used in the treatment of inflammatory bowel disease.

Balsalazide is the prodrug of mesalazine. The active drug is released from balsalazide by bacterial enzymes in the colon.

Very little balsalazide is absorbed after oral administration.

Mesalazine is absorbed, but is rapidly metabolised and excreted in the urine.

Balsalazide has been compared with mesalazine in a double-blind trial. Patients with acute ulcerative colitis were treated for up to 12 weeks. More patients taking balsalazide went into remission. At the end of the study 62% were in remission compared to 37% of the patients taking mesalazine.¹

This trial continued as a study of balsalazide and mesalazine in maintenance treatment. Although 58% of both treatment groups were in remission after a year, fewer patients taking balsalazide relapsed in the first three months. They also had more symptom-free days and nights.²

The adverse effects of balsalazide and mesalazine are similar. During the study of acute ulcerative colitis only half the patients treated with balsalazide experienced adverse effects compared to 70% of the patients taking mesalazine.¹ However, during maintenance treatment both drugs were associated with adverse effects in more than 60% of patients.²

Adverse effects include headache, diarrhoea, nausea and vomiting. Balsalazide should not be given to patients who are allergic to salicylates. Any unexplained bleeding or bruising is an indication for a blood test to look for a blood dyscrasia.

The newer aminosalicic acid derivatives were designed to overcome the problems associated with drugs such as sulfasalazine. A Cochrane review has, however, questioned if the newer drugs have a clinical advantage over sulfasalazine for inducing remission.³ Another Cochrane review has found that the newer drugs are inferior to sulfasalazine for maintenance treatment.⁴ The use of balsalazide is therefore restricted to patients who are intolerant of sulfasalazine.

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Bevacizumab

Avastin (Roche)

100 mg/4 mL and 400 mg/16 mL in single-dose vials

Approved indication: metastatic colorectal cancer

Australian Medicines Handbook section 14.3.4

Many patients with colorectal cancer will develop metastatic disease. This is difficult to treat and has a very poor prognosis, so new therapies are being studied. One approach is to inhibit the new vessels the tumours need to grow. This can be attempted by inhibiting vascular endothelial growth factor, which is increased in metastatic disease.

Bevacizumab is a genetically engineered humanised monoclonal antibody against vascular endothelial growth factor. By binding to the growth factor, bevacizumab prevents it from binding to endothelial receptors.

In a study of 104 untreated patients with metastatic colorectal cancer bevacizumab was used in combination with fluorouracil and folinic acid. High and low doses of bevacizumab were tested in this study. The response rate, as judged by changes in tumour size, was 24% with the high-dose regimen and 40% with the low-dose regimen. This gave the low-dose regimen a statistically significant advantage over the 17% response rate seen in a control group of patients who received fluorouracil and folinic acid alone. Compared to the control group, patients given the combination containing the low dose of bevacizumab also had a significantly longer median time before their cancers

progressed (9 versus 5.2 months). Their median survival was 21.5 months compared to 13.8 months in the control group.¹ Following this trial, the low dose of bevacizumab (5 mg/kg) was studied in addition to a regimen containing irinotecan, fluorouracil and folinic acid. The four drugs were given to 402 patients with previously untreated metastatic disease and the results were compared with those of 411 patients given the three-drug regimen plus a placebo. Overall the response rate was 44.8% in the bevacizumab group and 34.8% in the control group. The progression-free survival was 10.6 months with bevacizumab compared with 6.2 months. There was also a significant difference in median survival time; 20.3 months in the bevacizumab group versus 15.6 months in the control group.²

Bevacizumab has to be diluted and given as a slow intravenous infusion once every 14 days. The antibody has a half-life of approximately 20 days.

Although bevacizumab improves survival by a few months it increases the risks of adverse effects. In the phase 3 trial there were significantly more serious adverse events in the patients taking the bevacizumab regimen than in those taking irinotecan, fluorouracil and folinic acid (84.9% versus 74%). Bevacizumab was associated with increased leucopenia, diarrhoea and hypertension.² Although there is a risk of venous and arterial thrombosis, including stroke and myocardial infarction, there is also a risk of fatal haemorrhage in patients taking regimens that include bevacizumab. The gut perforations which can occur with bevacizumab² may also be fatal. As wound healing may be affected, treatment should not begin until at least a month after surgery. Proteinuria is another problem and if the nephrotic syndrome develops treatment should be stopped. Congestive cardiac failure has also been reported.

Bevacizumab is approved for use with fluorouracil and folinic acid, or with fluorouracil, folinic acid and irinotecan.

Further studies are investigating the addition of bevacizumab to regimens containing oxaliplatin. Although genetic engineering is increasing treatment options, the best regimen is not yet clear.

T T T manufacturer provided all requested information

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Cetuximab

Erbitux (Alphapharm)

2 mg/mL in 50 mL vials

Approved indication: metastatic colorectal cancer

Australian Medicines Handbook section 14.3.4

Antineoplastic antibodies such as rituximab and trastuzumab act on cancer cells by binding to target antigens.¹ Cetuximab is a genetically engineered chimeric monoclonal antibody which binds the epidermal growth factor receptor. The gene for this receptor is overexpressed in many patients with colorectal cancer and is associated with a poor prognosis. By binding to the receptor, cetuximab blocks the action of epidermal growth factor with the aim of reducing the growth and viability of tumour cells.

Cetuximab is given by a slow intravenous infusion once a week. The pharmacokinetics of cetuximab vary with the dose. At higher doses there is a decreased clearance and increased half-life. At the recommended doses cetuximab has a half-life of 80–120 hours.

A randomised, open-label trial compared cetuximab alone or in combination with irinotecan in 329 patients with metastatic colorectal cancer. All the patients had tumours with epidermal growth factor receptors and their tumours had progressed despite previous treatment with irinotecan. Approximately 11% of the patients given cetuximab and 23% of the patients given the combination had some response to treatment, as judged by imaging studies. Although the median time for the disease to progress was longer with the combination (4.1 months versus 1.5 months), this therapy had no significant survival advantage over cetuximab alone. The median survival was 8.6 months with combination therapy and 6.9 months with monotherapy.²

During the study 80% of the patients developed an acne-like skin reaction. This was severe in 5.2% of the patients taking cetuximab and in 9.4% of those taking cetuximab with irinotecan.² Premedication with an antihistamine is recommended because of the risk of a hypersensitivity reaction to an infusion of cetuximab. Dyspnoea has developed in 25% of patients given cetuximab. This has been severe in approximately 10% of patients. Those given cetuximab in combination with irinotecan are prone to diarrhoea and neutropenia. Blocking the epidermal growth factor receptor may delay wound healing.

After irinotecan has failed adding cetuximab induces a greater response than giving cetuximab alone. This suggests that cetuximab somehow enhances the effect of irinotecan. There is therefore a need to compare cetuximab with other drugs, such as oxaliplatin, which can be given to patients with irinotecan-refractory disease.

Although cetuximab has been approved for monotherapy and for use in combination with irinotecan, combined therapy is more likely to be useful for metastatic disease that has

progressed. Cetuximab should not be prescribed for patients whose colorectal tumours do not have overexpression of the epidermal growth factor receptor.

manufacturer did not respond to request for data

References [†]

1. Ward R. Antineoplastic antibodies – clinical applications. *Aust Prescr* 2003;26:141-3.
2. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-45.

Ciclesonide

Alvesco (Altana Pharma)

metered dose inhalers delivering 80 microgram or 160 microgram per actuation

Approved indication: asthma prophylaxis

Australian Medicines Handbook section 19.2

Inhaled corticosteroids can have an important role in helping patients with asthma achieve their best lung function.

Ciclesonide is a non-halogenated glucocorticosteroid which is claimed to have a finer aerosol than other drugs, so less of the dose is deposited in the oropharynx. In the lung, ciclesonide is metabolised to its active metabolite which has a higher affinity for glucocorticoid receptors. Although ciclesonide has a different structure, it still acts like other inhaled corticosteroids by reducing bronchial hyperreactivity and inflammation in the airways.

The active metabolite is metabolised by cytochrome P450 3A4, so drugs which inhibit this enzyme may increase plasma concentrations of the metabolite. The clinical significance of this interaction with inhaled ciclesonide is unclear. Ciclesonide and its metabolites are mainly excreted in the faeces.

The effect of ciclesonide has been compared with placebo in a double-blind crossover trial of 13 asthmatic patients given an allergen challenge. After inhaling powdered ciclesonide for a week before the challenge the patients' forced expiratory volumes (FEV₁) decreased significantly less than they did after one week of placebo.¹

Although ciclesonide is more active than placebo it is unclear if it has any greater efficacy than other drugs such as budesonide. The product information says there have been 16 trials of ciclesonide, but few of them seem to have been published in full by peer-reviewed journals. As only five studies of 12 weeks' duration are briefly summarised in the product information, it is difficult to assess the long-term effectiveness of ciclesonide in asthma.

In theory, the deposition of most of the dose in the lung and ciclesonide's lower affinity for the glucocorticoid receptors should reduce some of the problems associated with inhaled

corticosteroids. The common adverse effects of ciclesonide include hoarseness and bronchospasm, but the incidence of long-term adverse effects such as adrenal suppression and cataracts is unknown. It is not approved for use by children under 12 years old.

Although ciclesonide has the convenience of a once-daily dose, its place in therapy is unclear. Until more data are made available for scrutiny, there seems to be little justification for doctors to add ciclesonide to their choice of inhaled corticosteroids.

manufacturer did not respond to request for data

Reference

1. Larsen BB, Nielsen LP, Engelstätter R, Steinijans V, Dahl R. Effect of ciclesonide on allergen challenge in subjects with bronchial asthma. *Allergy* 2003;58:207-12.

* 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 Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

Patient support organisation

Ménière's Support Group

(See 'Dealing with dizziness', page 94)

The Ménière's Support Group assists with providing community support for people who have Ménière's disease. It produces a quarterly magazine and holds meetings for members, their families and friends. Resources such as fact sheets, information packs and videos are available from the state offices, from the Ménière's Resource and Information Centre and via an online catalogue (www.menieres.org.au). Health professionals interested in learning more about Ménière's disease are encouraged to use these resources.

At present three state offices provide support and services to all states.

Contacts

Website: www.menieres.org.au

Email: info@menieres.org.au

Ménière's Support Group of Victoria Inc. and Ménière's Resource and Information Centre

1254 Nepean Highway (cnr. Cobb Rd.)

MT ELIZA VIC 3930

Phone: (03) 9775 2972

Fax: (03) 9787 2963

Enquiries from South Australia and Western Australia should also be directed here.

Ménière's Support Group of NSW Inc.

PO Box 2414

BOWRAL NSW 2576

Phone: (02) 4861 3751

Email: info@menieresnsw.org.au

Enquiries from Queensland and Northern Territory should also be directed here. There are also offices in Sydney, Newcastle, Dubbo and Mudgee.

Ménière's Support Group of Tasmania Inc.

PO Box 202

MOONAH TAS 7009

Phone: (03) 6234 1494

Website: www.msgtas.org.au

Answers to self-test questions

- | | | | |
|----------|---------|----------|----------|
| 1. True | 3. True | 5. False | 7. False |
| 2. False | 4. True | 6. True | 8. False |

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