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EDITORIAL

# Palliative care for non-malignant disease?

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**Index words: cancer, pulmonary disease, heart failure.**

*(Aust Prescr 2003;26:98–9)*

The Minister for Health and Ageing recently announced $4.5 million of Commonwealth funding for palliative care programs in Australia. Importantly, these funds and the programs they support are not constrained within the traditional boundaries of palliation for patients with terminal malignant disease. Indeed, the new language for palliative care in Australia describes 'quality care' for **all** people who are dying.

Palliation beyond malignant disease has many far-reaching implications. In the future clinicians will no doubt have to apply these programs in an environment of limited resources and funding. The effectiveness and impact of these new programs will need to be evaluated as they are presently unknown. For the moment, however, it is important to understand why certain patients with non-malignant disease would benefit from palliation at the end of life and how they can be readily identified.

We are currently experiencing an epidemic of old and fragile patients with chronic cardiorespiratory disease. Congestive heart failure is the commonest cause of emergency hospitalisation in those aged over 65 years[1], while chronic obstructive pulmonary disease (COPD) accounts for around one in 20 deaths.[2] Importantly, at this stage, neither disease is curable.

Patients with end-stage heart failure typically have an extremely poor quality of life, punctuated by frequent hospitalisations and a prognosis that is comparable to that of common malignancies.[1] Dyspnoea, confusion, pain, anxiety and depression are very common during the last few days of life. Once cognisant of the terminal nature of their illness, many patients would prefer 'comfort care' and do not wish active resuscitation. Despite this there is a relative lack of patient (and carer) preparation for death.

One study specifically compared the illness trajectories, needs and pattern of health care utilisation of patients 'dying' from heart failure or lung cancer.[3] The illness trajectory of lung cancer was much more predictable, while the management of heart failure was characterised by poor co-ordination and a lack of continuity of care.[3] Another study found that although COPD has a similar prognosis to lung cancer, it is often associated with a poorer quality of life and more emergency hospitalisations.[2] Moreover, 40% of patients suggested they wanted more information about their illness, but very few requested detailed information, implying that a more accurate description of their prognosis would be distressing.[2]

It is clear, therefore, that many patients with end-stage cardiorespiratory disease deserve greater attention to palliation. However, given the inherent need to ration finite healthcare resources, a pragmatic approach to implementation is required.

There is strong argument for offering palliation to anyone who, in all probability, is **likely** to die within the next 12 months.[1] It is particularly important, therefore, for the clinician to remember to apply the principles of palliative care on the basis of 'need' rather than 'diagnosis'.

Clearly, extending palliation beyond malignancy raises a number of complex issues. Clinicians will be forced to overcome a natural desire to be optimistic and to avoid alarming patients unnecessarily with thoughts of impending death. It is in the best interests of the patient if the clinician comes to the conclusion that all therapeutic options are exhausted – even if the patient has not reached the same conclusion. Despite the problem of 'denial' at the end of life, it is the frequent wish of patients that the doctor begins discussions about death.[2] However, there is an inherent problem in predicting the illness trajectory of COPD and heart failure.

## In this issue ...

Although the new drugs for lung cancer discussed by Michael Boyer may help some people, patients will still need palliative care. However, according to Simon Stewart we should not be restricting palliative care to patients with cancer. Many patients with medical illnesses also have avoidable suffering before death.

Many deaths in the Aboriginal community occur prematurely. Richard Murray relates some of the important prescribing issues for indigenous Australians. Improvements in Aboriginal health will require legislative changes as well as good prescribing.

While Spiros Fourlanos and Peter Greenberg educate us about the causes of a low sodium concentration, John Attia reminds us that diagnostic tests are not infallible.

For example, in the SUPPORT Study some patients with heart failure had been predicted to have a greater than 50% chance of surviving six months, but died just three days later.[4]

Not knowing how long the patient will live creates a situation of uncertainty that can, in theory, 'paralyse' doctors, potentially preventing them from implementing palliative care.[1] In all probability there is no solution to such 'treatment paralysis' without specific, professional guidelines and an increase in consumer expectations to prompt appropriate end-of-life care.

Palliative care represents holistic management that has moved beyond medical cure. It focuses on the physical, psychological, social and spiritual problems of the patient at the end of their life.[2] In simple terms, it equates to providing a good quality end to life by whatever means possible.[1] This includes enabling people to put their affairs in order and to prepare for the future.

Although palliation has historically focused on terminal malignancy, most people who are physically deteriorating and approaching the end of life experience similar problems. Four main issues are common to all patients who are expected to live less than 12 months:

- deficits in basic self-care
- emotional distress
- pain and chronic symptoms
- malnutrition.[5]

In COPD and heart failure, persistent dyspnoea, with associated limitations on all activities of daily living, is particularly distressing. Dealing with such problems requires a multidisciplinary approach combined with the core palliative care values of open and sensitive communication, a whole patient and carer approach, attention to symptom control and therapeutic dialogue.

Although it is clear we are responding inadequately to an increasingly important issue seen in clinics and wards all over the developed world, we are currently witnessing a shift in our thinking about extending palliative care to non-malignant, terminal disease. Applying palliation on the basis of 'need' rather than 'diagnosis' raises a number of difficult issues for clinicians and their patients alike. However, the potential benefits of palliative care can ensure a quality end of life for more individuals, and should not be denied on the basis of being too hard.

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*Professor Stewart holds the National Heart Foundation/ Roche Chair of Cardiovascular Nursing.*

## Self-test questions

*The following statements are either true or false (answers on page 119)*

1. Patients with chronic obstructive pulmonary disease may have a poorer quality of life than patients with lung cancer.
2. Predicting the duration of survival is harder to do for patients with congestive heart failure than for patients with lung cancer.

# 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.

### Hypertension: how low to go?

Editor, – Articles which challenge accepted orthodoxy are usually good reading, and Suzanne Hill's article on hypertension (Aust Prescr 2003;26:53-5) is no exception. A number of interesting points emerge from her critique of the HOT study.

I take it that Table 1 deals with the whole population studied, including the 20% who were no longer using felodipine by the end of the study. The reason for cessation was not given in the study, but if it was due to adverse effects (few people enjoy having swollen legs) the results do not flatter felodipine as a first-choice drug.

Although the risk reductions shown in Table 1 all fail to reach statistical significance, seven out of nine favour the target groups with higher diastolic blood pressure. It is very hard indeed to see how they can be interpreted as showing 'the benefits of lowering the diastolic blood pressure down to 82.6 mmHg'. Dr Hill rightly rejects that conclusion.

Perhaps the study can be classified with the many which assess the effect of a single treatment regimen on a single selection of end-points (or surrogate end-points). The authors of such studies seem to forget that it is possible to die of something other than the disorder they are investigating. Indeed, the more proficient we become at preventing death

from the big killers, the more of us will be left to die of something more painful, prolonged and expensive, such as cancer or dementia. Dr Hill rightly remarks that we should discuss quality issues with our patients, and not merely try to preserve them from this or that disease. In other words, we should treat patients, not statistics.

Dr Hill tells us that the diabetic sub-group definitely benefited from a more intensive effort to reduce their diastolic blood pressure. That means that the non-diabetic sub-group contributed more than their fair share to the non-benefit (or harm). It would be interesting to know if any of the comparisons in the non-diabetic sub-group showed significant harm.

Half the study population was given aspirin and the other half placebo. It would be useful to know if aspirin, used as primary prevention, contributed in any way to the good or bad effects, and if so in combination with which antihypertensives.

Bringing down the blood pressure with a calcium channel blocker may not be the same as bringing it down with (say) an ACE inhibitor. It is risky, therefore, to infer from the HOT study (or any other) that setting a target blood pressure, and achieving it **by any means** is a good or bad idea.

Alasdair Livingston
Surgeon
Mitcham, SA

Editor, – The hypertension article in *Australian Prescriber* (Aust Prescr 2003;26:53-5) reports the HOT study in which the emphasis is on the diastolic blood pressure whereas a recent report, of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure in the USA, emphasises the systolic blood pressure. I understand current thinking is that emphasis should be on the systolic blood pressure as, if the systolic blood pressure is the aim of treatment the diastolic blood pressure will be satisfactory. Emphasis on diastolic blood pressure can leave the patient with a systolic blood pressure which is at a dangerous level.

John H. Hill
General practitioner
Moruya, NSW

*Dr Suzanne Hill, the author of the article, comments:*

Dr Livingston identifies a number of interesting points around the interpretation of data from blood pressure trials. One of the difficulties about writing review articles in this area at the moment is that the literature is moving very quickly, with the recent publication of two more large clinical trials (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Second Australian National Blood Pressure Study (ANBP2)) as well as the publication of meta-analyses.[1]

Specific issues raised by Dr Livingston that I am not able to address include the question of whether there was particular harm in the sub-group of patients without diabetes. This is not reported in the original paper. The question of the role of aspirin would also have to be addressed by further analyses of the data, and indeed this is being addressed by ongoing studies[2] looking at the combinations of treatment for cardiovascular disease. The question of class effects and therapeutic group effects is a topical area and may need to be addressed by an article that more comprehensively reviews the current 'state of play' in thinking about treatment of hypertension.

Dr Hill noted the question of identifying risk based on systolic blood pressure versus diastolic blood pressure. This was not a question addressed by the HOT study, as he rightly identifies, and the answer would require a comprehensive review of current blood pressure literature to address completely.

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## Serotonin syndrome

Editor, – I would like to reinforce the message about the spectrum of serotonin toxicity (Aust Prescr 2003;26:62–3). This term represents a more productive descriptive model than serotonin syndrome because there is a spectrum progressing from serotonergic adverse effects through to toxicity (hyperthermia and death). Severity is proportional to the degree of elevation of serotonin concentrations. The loose usage of the term serotonin syndrome continues to produce great confusion.[1,2] For instance, the frequently made statement 'serotonin syndrome is rare' is nonsensical because it is like saying 'poisoning is rare in those who do not ingest poisons'.

General physicians will be reassured to be reminded that life-threatening/fatal serotonin toxicity related to therapeutic drugs has been reported only when monoamine oxidase inhibitors (MAOIs) are combined with serotonin reuptake inhibitors.

I maintain a current synopsis about serotonin toxicity and implicated drugs (i.e. what drugs act as serotonin reuptake inhibitors, or MAOIs, in humans) at www.psychotropical.com/SerotoninToxicity.doc I also draw your readers' attention to other original Australian research.[3] The 'HATS' database continues to make a valuable contribution to all aspects of serotonin toxicity and the interesting deductions that ensue.[4]

Clinical advice from experts may be accessed via the toxicology services whose 24 hour telephone number in Australia is 13 11 26.

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Editor, – The review of serotonin syndrome (Aust Prescr 2003;26:62-3) explores drug interactions as a cause of serotonergic toxicity. We have noticed a significant number of enquiries regarding the concomitant use of the commonly used migraine medication sumatriptan and selective serotonin reuptake inhibitors (SSRIs). The article implies that any combination of serotonergic drugs should be avoided. While sumatriptan is regarded as 'serotonergic', the isolated case reports of apparent serotonin syndrome are not convincing and do not, in our clinical practice, constitute a reason for avoiding the combination.

A review failed to locate clinical evidence supporting a contraindication for sumatriptan and SSRIs.[1] Sumatriptan, a 5-HT agonist, does not appreciably cross the blood-brain barrier and has a significantly lower affinity for 5-$HT_{1A}$ than for 5-$HT_{1D}$ receptors, thereby limiting its intrinsic ability to mediate a serotonergic response. Nevertheless, as the *Australian Prescriber* article suggests, patients should be educated about the possibility of interactions between serotonergic drugs. Before starting therapy, they also need to be informed of the signs and symptoms of serotonin toxicity and what to do if an adverse reaction develops.

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*Dr M. Hall and Dr N. Buckley, the authors of the article, comment:*

As stated in our original article, sumatriptan has been linked to mild serotonin syndrome in a number of case reports. We deliberately did not include it in the table of drugs implicated in severe serotonin syndrome. We do not believe that the article suggests that any combination of serotonergic medications should be avoided, but merely points out that the potential for such an interaction exists, and prompts education of the patient, and the physician, about these possibilities.

## Radiosynovectomy in rheumatoid arthritis

Editor, – 'Disease modifying drugs in adult rheumatoid arthritis' (Aust Prescr 2003;26:36–40) is an informative article, however, I would appreciate comments on the therapeutic applications of beta-emitting radionuclides like Holmium-166.

M.A. Taher
Director, Centre for Nuclear Medicine & Ultrasound
Bangladesh Atomic Energy Commission, Rangpur-5400
Bangladesh

*Dr Anita Lee and Dr Kevin Pile, authors of 'Disease modifying drugs in adult rheumatoid arthritis', comment:*

Intra-articular instillation of a radioactive isotope, to perform a non-surgical synovectomy of persistently inflamed solitary joints, has been proposed as an adjunctive therapy for rheumatoid arthritis and spondyloarthritis. The theoretical ideal agent is a beta-emitter that can be delivered in a colloidal or particulate form, that is small enough to be phagocytosed by the macrophage synovial lining cells, yet large enough to reduce systemic absorption. In practice radiosynovectomy has primarily been trialled in knee synovitis so as to ensure intra-articular placement. Yttrium 90 and Dysprosium 165 are available for intra-articular use in Australia. Holmium 166 is a short half-life beta-emitter that has been used overseas.

Despite its theoretical utility, a systematic review of Yttrium 90 radiosynovectomy of the knee in patients with rheumatoid arthritis found that there was little support for its use, in comparison to saline or corticosteroid injections.[1]

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## Withdrawal of useful drugs from the market

Editor, – The editorial 'Withdrawal of useful drugs from the market' (Aust Prescr 2003;26:50–1) makes a cogent observation about discontinuation of old drugs. The newer antidepressants, antipsychotics, antihypertensives and drugs for diabetes may have some advantages, but they are certainly not worth the high cost.

Most of the useful old drugs are included in the essential drugs lists of the World Health Organization or of developing countries. If it was compulsory for the drug manufacturers to inform people about the discontinuation of essential drugs, it would be easier for governments to make the drugs available as generics or as generic brands.

Wishvas Rane
Pune
India

Editor, – I found Dr Lyndon's editorial (Aust Prescr 2003;26:50–1) on the withdrawal of drugs very pertinent.

Dr Lyndon correctly states there are many reasons for pharmaceutical companies to discontinue supply of a drug. Although their reasons are generally understandable, this does not help those patients for whom the remaining commercially available alternatives are less effective. I would like to advise prescribers that there is a route available in Australia, perhaps not widely known, to obtain most discontinued medication.

Compounding pharmacies prepare and supply medication (known as extemporaneous preparations) for individual patients. As long as the pharmacists can source raw material and do not infringe any patents, they are able to produce

virtually any medication. They can produce medication that is no longer available here or that is available overseas but has not been released in Australia (often due to a perceived lack of sufficient demand).

I believe Dr Lyndon is quite right in his concerns that there is no co-ordinated process involving all interested parties, to discuss the discontinuation of products. Such a forum would certainly be a worthwhile development.

Although not a perfect alternative (the cost of individually compounded medication will be higher), prescribers will now be aware that all is not lost if an effective treatment is removed from the marketplace.

Alan Hewitt
General manager
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Bondi Junction, NSW

## Declaration of interest/affiliation

Editor, – Many letter writers declare their affiliations. Sometimes their significance is obscure to me. For example, what sort of a body is 'Medicines Australia' (Aust Prescr 2003;26:51)? It sounds official and important but the title is suspiciously trendy, like Cricket Australia rather than the Australian Cricket Board. It has a whiff of spin doctoring and public relations about it. Is it an industry lobby group perhaps, or maybe the antipodean arm of Médecins Sans Frontières? We need to know if we are to judge the communication.

G. Wise
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*Editor's note:*

Medicines Australia is the new name for the Australian Pharmaceutical Manufacturers Association. Its mission statement is 'to create a favourable environment for the profitable growth of the prescription pharmaceutical industry in a socially responsible manner for the benefit of the Australian community'.

## And next: a flask of wine for Daddy? *

Editor, – Last year I sent a complaint to the Australian Self-Medication Industry (ASMI) about the promotion of Ponstan (mefenamic acid) by Pfizer in community pharmacies. Pfizer was providing dispenser units with Ponstan packs at the bottom, lip gloss jars at the top, and the claim 'Buy Ponstan and receive a free lip gloss'. I stated in my letter of complaint that 'If ASMI authorises the use of gifts to consumers as promotional techniques, it sets a precedent for other abuses of the system, e.g. giving away a Teddy Bear with every sale of children's paracetamol'. Pfizer responded that 'the complaint is without merit and that the promotion is appropriate'. ASMI dismissed my complaint on the ground that there was no provision in their code of practice to ban this type of promotion. They stated they would consider amending their code in this regard, but their new code released in March 2003 has not been changed.

I was amazed this morning to find in a My Chemist's shop that Pfizer had taken seriously the idea of teddy bears and displayed a full box of colourful Benadryl Teddy Bears with the claim 'Free Benadryl Bear with any Benadryl purchase'. This kind of promotion encourages the public to equate medicines with ordinary articles of commerce. Such promotion is inappropriate for responsible health professionals and encourages unprofessional behaviour by community pharmacists. Pharmacist organisations, pharmacy boards and regulatory authorities should take immediate action to stop this type of promotion as the self-medication industry appears incapable of regulating its members properly.

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Quality Use of Medicines and Pharmacy Research Centre
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Member of Healthy Skepticism

* In 1995 in Peru Parke-Davis promoted its cough and cold remedy Sinutab with the promise to pharmacists of a complimentary bottle of red wine to celebrate Father's Day if they sold three boxes of Sinutab Maximum Strength or Sinutab Non-Drowsy.[1]

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# Drug therapy of lung cancer

*Michael J. Boyer, Head, Department of Medical Oncology, Sydney Cancer Centre, Royal Prince Alfred Hospital, Sydney*


## SYNOPSIS

**Lung cancer is the commonest cause of death from cancer in Australia. Almost all patients with small cell lung cancer are given chemotherapy either alone or in combination with radiotherapy. The use of chemotherapy in the management of metastatic non-small cell lung cancer has increased over the past decade. It can prolong survival and improve quality of life, when compared to best supportive care. Chemotherapy has an expanding role in the management of earlier stage disease and is now frequently included in combined modality treatment programs.**


**Index words: antineoplastics, chemotherapy.**

*(Aust Prescr 2003;26:103–5)*

## Introduction

Each year almost 7000 Australians die as a result of lung cancer, making this the commonest cause of death from cancer. Although efforts to reduce the proportion of the population who smoke have been successful in reducing the incidence of the disease in men, the number of new cases in women continues to rise. Up to 25% of patients present with early stage, localised disease that is amenable to surgical treatment. However, for the remainder, treatment often involves the use of chemotherapy, either as part of a potentially curative combination of therapies or as part of palliative therapy.

There are two major types of lung cancer. These are small cell lung cancer and non-small cell lung cancer. Small cell lung cancer accounts for approximately 20% of all lung cancer and is a discrete histologic and clinical entity. Non-small cell lung cancer, which accounts for the remaining 80% of cases, is a term that encompasses several histologic types of tumour. These include adenocarcinoma (also including bronchoalveolar carcinoma), squamous cell carcinoma and large cell carcinoma. As these tumours all behave in a similar way, their management is identical.

## Chemotherapy for non-small cell lung cancer

Over the past decade there has been a marked increase in the use of chemotherapy. This has occurred as a consequence of two meta-analyses which showed that chemotherapy prolonged survival in metastatic disease[1,2], the availability of several new anticancer drugs[3] and a recognition that combined modality treatment which includes chemotherapy produces better outcomes in patients with locally advanced disease.

The newer drugs, which are associated with higher response rates and less toxicity than older drugs, include docetaxel, gemcitabine, paclitaxel and vinorelbine. However, none of these drugs was included in the meta-analyses. The newer drugs are usually used in combination with a platinum drug (either cisplatin or carboplatin) or, rarely, with one another. They may be used alone in less fit patients. Most people can be treated as outpatients. The usual administration schedules of these drugs, as well as common adverse effects, are summarised in Table 1. Febrile neutropenia is the most serious potential complication of chemotherapy for non-small cell lung cancer. This requires prompt assessment and management with broad-spectrum intravenous antibiotics.

All of the newer drugs produce responses (reduction of more than 50% in the cross-sectional area of tumours) in 15–25% of patients when they are used alone. Combinations which include cisplatin or carboplatin produce slightly higher response rates. Response rates are not good indicators of patient benefit. Therapeutic decisions should therefore not be based solely on response rates, but should take into account survival, control of symptoms, and quality of life.

### *Metastatic non-small cell lung cancer*

Metastatic (stage IV) disease is incurable so the goals of treatment are to prolong life and palliate symptoms. Although early randomised trials failed to show a significant effect of chemotherapy on survival compared to best supportive care,

*Table 1*

**Drugs used in the treatment of small cell and non-small cell lung cancer**

| *Drug* | *Usual duration and schedule for intravenous infusion* | *Commonest adverse effects* |
|---|---|---|
| Carboplatin | 1 hour every 21 days | Thrombocytopenia, neutropenia, anaemia |
| Cisplatin | 1–2 hours every 21 days | Nausea, vomiting, renal impairment, anaemia, neuropathy, tinnitus, hearing loss |
| Docetaxel | 1 hour every 21 days | Neutropenia, fluid retention, neuropathy, alopecia |
| Etoposide | 1 hour daily for 3 days every 21 days | Neutropenia, alopecia |
| Gemcitabine | 30 minutes every 7 days | Thrombocytopenia, lethargy |
| Paclitaxel | 3 hours every 21 days | Neutropenia, neuropathy, allergic reactions, alopecia |
| Vinorelbine | 5–10 minutes every 7 days | Neutropenia, neuropathy, pain during infusion, erythema at infusion site |

more recent studies, and two meta-analyses, have found that chemotherapy produces a modest prolongation of life. Just as important has been the demonstration of improvements in symptoms and quality of life in patients receiving treatment.[4,5] This is particularly the case for the symptoms patients with lung cancer commonly experience such as haemoptysis, shortness of breath, cough and chest pain.

One of the principal arguments against the use of chemotherapy has been the toxicity associated with many of the older drugs, such as cisplatin, vindesine and mitomycin. More modern drugs such as paclitaxel, docetaxel, gemcitabine and vinorelbine all provide increased efficacy with reduced toxicity. The use of carboplatin in place of cisplatin, and the availability of more effective antiemetics such as the serotonin ($5HT_3$) antagonists, have also reduced the nausea and vomiting that previously had a negative impact on the quality of life of patients undergoing chemotherapy.

Most chemotherapy involves a combination of two drugs (Table 2). Randomised trials have shown that these combination regimens have better outcomes than single drugs do. Single drug regimens may be appropriate for older patients, or those with poorer performance status (for example those who are confined to bed for more than 50% of the day or those with severe comorbidity). There is no advantage in using more than two drugs. In addition, there is no single 'best' regimen; any of the combinations shown in Table 2 is an acceptable first-line treatment for metastatic disease.[6]

Newer oral drugs such as the epidermal growth factor receptor tyrosine kinase inhibitors are expected to come into routine use in the near future. Their efficacy and lower toxicity mean that they may have a future role in treating frail patients. However, randomised trials have failed to show a survival benefit when one of these drugs, gefitinib, is added to standard chemotherapy.

There has been a gradual improvement in the survival of patients with advanced non-small cell lung cancer following chemotherapy. The median survival and one-year survival rate improved from four months and 15% with supportive care alone, to six months and 25% with early chemotherapy regimens. Modern chemotherapy usually results in a median survival of 10 months and a one-year survival rate of 35–40%, with the two-year survival rate up to 25% in several recent clinical trials.[7] While these are only modest improvements in outcome, patients regard them to be of value. Patients whose performance status is poor derive little benefit from chemotherapy.

*Table 2*

**Commonly used combinations for treating non-small cell lung cancer**

| |
|---|
| Cisplatin + gemcitabine |
| Cisplatin + vinorelbine |
| Cisplatin + docetaxel |
| Carboplatin + paclitaxel |
| Carboplatin + gemcitabine |

*Table 3*

**Treatment outcomes for small cell and non-small cell lung cancer**

| *Stage* | *Treatment* | *Median survival (months)* | *Long-term survival* (%)* |
|---|---|---|---|
| Non-small cell lung cancer | | | |
| IIIA† | chemotherapy/surgery | 24 | 30 |
| IIIB‡ | chemotherapy/radiotherapy | 12–18 | 10 |
| IV | chemotherapy | 10 | < 5 |
| Small cell lung cancer | | | |
| Limited | chemotherapy/radiotherapy | 18–24 | 20–25 |
| Extensive | chemotherapy | 10–12 | 5 |

* percentage of patients still alive 3 to 5 years after diagnosis
† involved ipsilateral mediastinal lymph nodes
‡ involved contralateral mediastinal lymph nodes

In recent years there has been an increased interest in second-line chemotherapy (treatment given when the disease has progressed during or after initial chemotherapy). In a randomised trial, docetaxel has improved survival when compared to best supportive care in previously treated patients with good performance status. Non-randomised data also exist for gefitinib, showing symptom improvement in up to 40% of such patients.

***Locally advanced non-small cell lung cancer***

The cancer in patients with locally advanced (stages IIIA and B) disease is confined to the thorax, but has spread to involve the mediastinal lymph nodes. Traditional management approaches have used surgery or radiotherapy for these patients, but the results were poor with only 5–20% of patients surviving for 3–5 years. Recently, combined modality treatment has become more common.

Giving chemotherapy either before surgery and radiotherapy, or concurrently with radiotherapy, has resulted in modest improvements in survival (Table 3). One of the combination chemotherapy regimens is usually used and no specific combination has superiority. Three to four cycles of chemotherapy are usually given over 9–12 weeks before surgery, or concurrently with radiation therapy.

The addition of chemotherapy to the management plan for these patients also adds to the toxicity of treatment. In addition to the toxicities of chemotherapy itself, there are adverse effects that result from its combination with surgery and radiotherapy. Surgical morbidity is increased following chemotherapy and this may lead to small increases in mortality, however this is usually not excessive in the hands of experienced thoracic surgeons. Patients receiving chemotherapy and radiotherapy concurrently are at an increased risk of complications such as radiation pneumonitis and oesophagitis. These complications are usually self-limiting, but can be the cause of significant morbidity.

Some patients with stage IIIB disease present with substantial weight loss or a pleural effusion. Their outlook is poor, with

the disease behaving more like metastatic than locally advanced disease. Consequently, treatment for these patients should be identical to that given to patients with stage IV disease.

## Small cell lung cancer

Two features of small cell lung cancer result in it being treated quite differently to non-small cell lung cancer. Firstly, the disease has a propensity for early and widespread metastases; even patients with disease that is clinically localised to the thorax are likely to be harbouring occult metastases. Secondly, small cell lung cancer is extremely chemo- and radiosensitive. The staging of patients is different from that of patients with non-small cell lung cancer. Patients with a small cell cancer confined to one hemithorax (including the ipsilateral supraclavicular fossa) are said to have limited disease while those with tumour beyond this have extensive disease.

### *Chemotherapy*

For patients with limited disease, a combination of intravenous chemotherapy and thoracic radiotherapy is the mainstay of treatment. Ideally, these modalities should be given simultaneously.[8] Usually patients are treated as outpatients with the combination of intravenous cisplatin and etoposide, given each day for three days. Four cycles of treatment are given, with a 21-day gap between each cycle. Radiation is given daily for approximately 4–5 weeks. Concurrent chemotherapy and radiotherapy results in increased toxicity, particularly in the elderly and those with comorbidities (e.g. coronary artery disease). In these patients, it is common to use a sequential approach, with the radiation treatment not given until the conclusion of all chemotherapy.

The rationale for the use of thoracic radiotherapy is that relapse usually occurs at the site of bulk disease (usually in the lung or mediastinum). Hence radiation is directed toward this site. By contrast, patients who present with extensive disease are at risk of relapse at any of the tumour sites, and so there is no reason to target any one location using radiotherapy. The usual management of these patients is with intravenous chemotherapy alone, using carboplatin and etoposide, given daily for three days. Up to six cycles of treatment are given, with each cycle planned to be 21–28 days apart, depending on the extent of treatment-induced myelosuppression. Treatment results in an improvement in symptoms and a prolongation in survival from the median of three months without therapy.

Although an oral formulation of etoposide is available, it is not widely used. There is substantial variability in absorption between patients leading to unpredictable haematological toxicity. This is reflected in the results of randomised trials comparing oral and intravenous use of etoposide, which show increased toxicity and worse outcomes in patients receiving oral therapy.

In contrast to non-small cell lung cancer, there has been little change in the drugs used to treat small cell lung cancer in the past decade and the prognosis is poor (Table 3). Although all of the newer drugs used for treating non-small cell lung cancer also have activity in small cell lung cancer, they have not resulted in improved outcomes. Recently, irinotecan, a camptothecin widely used in the management of colorectal cancer, has been shown to improve survival in extensive small cell lung cancer when used in combination with cisplatin. The results of this single randomised trial are awaiting confirmation, and this regimen is not yet in widespread use.

## Future directions

A large number of newer drugs are currently undergoing clinical trials for use in lung cancer. These drugs differ from conventional chemotherapy by targeting molecules involved in tumour growth including those responsible for intracellular signalling and new blood vessel growth (angiogenesis). Typically, they have fewer adverse effects than conventional chemotherapy, and generally may be administered orally. However, the evidence available from current studies suggests that they will need to be used in conjunction with chemotherapy rather than in place of it, but their exact place in management remains to be defined.

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## Self-test questions

*The following statements are either true or false (answers on page 119)*

3. The best combination of drugs for chemotherapy of metastatic non-small cell lung cancer is unknown.
4. Modern chemotherapy regimens for metastatic non-small cell lung cancer increase the median survival by twelve months.

# Prescribing issues for Aboriginal people

*Richard Murray, Medical Director, Kimberley Aboriginal Medical Services Council, Broome, Western Australia*


## SYNOPSIS

**Aboriginal people have higher rates of morbidity and mortality than other Australians and compare poorly to similar populations in other developed countries. In spite of this, access to medicines by Aboriginal people is poor, even for those living in urban areas. In remote areas there are different patterns of disease and bacterial infections are very common. The threshold for prescribing antibiotics is generally lower because Aboriginal patients are at higher risk of serious sequelae. Drug regimens should be simplified to increase the chance of successful treatment. Improving Aboriginal health will require reforms including improved access to and quality use of medicines, and legislative reform to support involvement of Aboriginal health workers in managing medicines.**


**Index words: antibiotics, drug therapy, National Medicines Policy.**

*(Aust Prescr 2003;26:106–9)*

## Introduction

> *'Our services are tired of seeing patients go without medicines and get really ill because they physically can't get to a chemist shop, or because they can't afford their medicines. They're also tired of seeing patients come back sicker because they didn't have the right people on hand to explain properly to them how to use the medicines, and so they didn't take them or they made mistakes with them.'*
>
> – The late Dr Puggy Hunter, October 2000

The statistics of Aboriginal ill health are familiar to many of us. These include the 20-year shortfall in expectation of life at birth, the three-fold excess of infant mortality and many other health disparities between Aboriginal and non-Aboriginal Australians.

What is not widely appreciated is how poorly Australia compares with other developed nations. While Aboriginal people have seen no improvement in all-cause standardised mortality over the last generation, rates for Maori fell by 41% in the 20 years to 1994 in New Zealand and by 28% for Native Americans in the USA.[1] In these countries, expectation of life at birth now approaches that of the general populations. Key policy differences in Australia include woefully confused responsibility for funding and service delivery between different levels of government, manifest underexpenditure on indigenous health care and essential services, and our lack of a treaty underpinning indigenous rights.[2]

## Mortality and morbidity

Over 70% of the excess mortality among Aboriginal people is accounted for by cardiovascular disease (26%), respiratory conditions (16%), injury and poisoning (15%) and diabetes (10%).[1] The striking feature of Aboriginal mortality is the massive excess of death in middle age – a profile almost without comparison in the world.[3]

Acute morbidity patterns in Aboriginal primary health care include a marked excess of infectious diseases related to crowding and poor environmental health (skin and middle ear infections, rheumatic fever, trachoma). There are also high rates of sexually transmitted infections which the available evidence suggests is related to poor access to treatment rather than behaviour.[4] Chronic morbidity is highly prevalent in Aboriginal communities. Diabetes affects about 10–30% of adults[4], and the prevalence of end-stage renal failure in many areas is 20-fold higher than in the general population and has been doubling every five years in northern and central Australia. There are regional variations in patterns of infectious diseases (such as trachoma) and substance misuse (for example intravenous drug use versus petrol sniffing), but patterns of chronic disease are reasonably consistent. Population mobility means that 'remote' conditions will often show up in urban areas and vice versa.

## Access issues

Despite the importance of medicines, given the massive excess of acute infectious and chronic disease, there are real problems with access. A review of Aboriginal access to medicines subsidised under the Pharmaceutical Benefits Scheme (PBS) documented major barriers for Aboriginal people that were remarkably consistent across urban, rural and remote communities.[5] Underuse of medicines is evidenced by the fact that government PBS expenditure per head is only a third of that spent on our mostly healthy and largely urban general population and a sixth of that spent on concession card holders.[6]

## Implications for prescribing practice

Access is one of several prescribing issues which need to be considered when selecting an appropriate treatment regimen.

### *Ensuring supply*

Of the four arms of Australia's National Medicines Policy[7] (community access; standards of quality, safety and efficacy; quality use; and a responsible and viable pharmaceutical industry) access is clearly the most problematic for Aboriginal

people. Noting 'substantial access barriers and evidence of under-use of medicines' by Aboriginal people, the policy commits all of us – government, industry, consumer and health professional groups – to do more. Barriers include distance, poverty, administrative matters (such as lack of evidence of a person's entitlement to concessional charges) and the attitudes and behaviour of service providers.

The expenditure data suggest that the conventional model of general practice prescribing/community pharmacy supply with co-payments and a safety net has largely failed Aboriginal people. As further evidence of this, most Aboriginal health services dispense medicines directly to patients by one means or other – by maintaining a dispensary or imprest stock or through an account with the local pharmacist. Ensuring that Aboriginal patients are actually able to get the medicine they need is a critical consideration for the prescriber.

… denying medicine to the sick, poor and marginalised is a dubious 'lesson' in self-reliance.

While some argue that supply of 'free medicine' might lead to waste and encourage dependency, denying medicine to the sick, poor and marginalised is a dubious 'lesson' in self-reliance. For many Aboriginal patients, there are cogent reasons for the prescriber to dispense pharmaceuticals at the point of provision of primary health care – better integration of care, the opportunities for involvement of Aboriginal health workers, and minimisation of cultural, educational, financial and transport barriers. At the very least, there is an obligation on the prescriber to help broker supply.

### *Simplifying dosing regimens*

Aboriginal patients commonly face difficulties with drug regimens. The demographic profile means that up to a third of the population are 10 years of age or less – which compounds the problem of securing or refrigerating medicines. Other barriers include educational disadvantage, poverty, shared crowded households and harsh environmental conditions.

For all these reasons, simplified once- or twice-daily dosing regimens or single dose treatments are often preferred. Benzathine penicillin is widely used. Antibiotic regimens requiring three or four doses daily are commonly simplified to twice daily with appropriate dose adjustment. The listing of azithromycin for genital chlamydia and trachoma has greatly improved the effectiveness of therapy for these conditions (and for Donovanosis – a rare but important cause of genital ulcer disease).

The use of simplified regimens is not confined to antibiotics. Injectable and implantable progestogens for contraception are in widespread use.

### *Infectious disease*

Prescribers should be aware of important differences in the epidemiology and microbiology of infectious diseases in the Aboriginal population. In general, there are lower thresholds for antibiotic treatment and antibiotic choices need to reflect the differing microbiological aetiology (Table 1).

### *Chronic disease*

Diabetes and hypertension commonly coexist with other 'metabolic syndrome' risk factors including dyslipidaemia. As renal failure is the commonest cause of diabetes-related death in Aboriginal populations, ACE inhibitors are typically first-line therapy for hypertension and are also used for normotensive people with diabetes and proteinuria.

'Non-compliance' is an unhelpful construct in the Aboriginal health context and is often inappropriately used to defend poor standards of practice. The difficulties Aboriginal people face in adhering to medication regimens are real. Prescribers need to make the effort to ensure there is full understanding of the reasons for and the nature of treatment as well as an assessment of likely barriers that patients will face. Aboriginal health workers have a particularly important role in this respect.

### *Brand substitution*

Aboriginal patients are used to a particular physical appearance of their medicines so brand substitution is a common cause of concern and confusion. Such changes should be avoided and careful explanation is required if substitutions are made.

## Legal framework

The morbidity of Aboriginal people has major implications for a medicines regulatory and supply system that aims to support the timely, safe and efficacious use of medicines. Dispensing by healthcare workers other than doctors or pharmacists is widespread in Aboriginal health care, particularly but not exclusively in rural and remote communities. This often involves standard treatments for infectious disease (for example sexually transmitted infections, otitis media, skin infections, rheumatic fever chemoprophylaxis) as well as support with chronic disease medication (patient education, use of dosage administration aids, issuing repeat prescriptions).

In the Aboriginal health setting, prescribers commonly confront the dilemma of quite reasonable and well-established medication practices by Aboriginal health workers and registered nurses that fall outside various laws and regulations. While there has been limited statutory reform to cover dispensing of prescription drugs by registered nurses in many jurisdictions, this still often falls short of what goes on in remote practice.

Only the Northern Territory and Queensland have provision for use of prescription drugs by Aboriginal health workers. For Aboriginal health workers, training and accreditation in use of medicines is of vital interest, because it is one of the few areas of health practice that is specifically regulated by statute. While legislation does not prevent Aboriginal health workers from assessing and treating patients, administering injections, performing venepunctures or taking cervical smears, the

*Table 1*

**Common infectious diseases in the Aboriginal population, and prescribing issues**

| *Disease* | *Issues* | *Typical antibiotic choices* |
|---|---|---|
| Otitis media | Otitis media is a massive public health problem. It causes deafness, educational disadvantage and suppurative complications. Nasopharyngeal colonisation with pathogenic bacteria in infancy (related to overcrowding and inadequate health hardware) sets Aboriginal children up for recurrent acute otitis media and chronic suppurative otitis media. Unlike the general population where a viral aetiology is common, Aboriginal children are an 'otitis-prone' group among whom bacterial pathogens (mostly streptococci) predominate. Chronic suppurative otitis media affects up to 30% of children and syringing and topical antibiotics are effective first-line therapy. | Oral amoxycillin<br>Dilute povidone-iodine syringing (gentle) and topical antibiotics (Sofradex or preferably ciprofloxacin) for chronic suppurative otitis media |
| Sore throat | Rheumatic fever rates for Aboriginal people in central and northern Australia are among the highest reported in the world. Sore throat should always be treated with an adequate course of antibiotics, regardless of clinical appearance. | Benzathine penicillin (single dose) |
| Pneumonia | Aboriginal people die of pneumonia at 10 times the rate of the general population.[4] Early empirical antibiotic treatment is vital as tragic deaths result when treatment is delayed beyond the 'point of no return'. Pneumococcal vaccination is effective prevention and should be offered to Aboriginal adults with predisposing conditions (including substance misuse, diabetes, renal and heart disease) as well as all those over 50 years of age. | Procaine or benzathine penicillin +/- oral amoxycillin<br>'Third generation' cephalosporins should be considered with diabetes and alcohol misuse. Cover for melioidosis should be considered in the tropical north. |
| Suppurative skin infections | Suppurative skin disease caused by Group A streptococci is common in northern and remote areas and is substantially related to endemic scabies. Treatment of individuals typically involves topical permethrin +/- penicillin. Mass community treatment with scabicide, as well as alleviation of crowding and improvement of water supply and ablutions, are effective disease control measures. | Benzathine penicillin (single dose)<br>Oral penicillins, macrolides or cephalosporins<br>Permethrin |
| Trachoma | Trachoma continues to be a problem in many remote Aboriginal communities. Management involves treatment of clinical cases with a single dose of azithromycin as well as treatment of the 'crèche' (care-givers and other close children). | Azithromycin (single dose) |
| Bacterial sexually transmitted infections | For the jurisdictions where indigenous status is captured in surveillance data (NT, SA and WA) some 70% of total syphilis and gonorrhoea cases and 40% of total chlamydia cases are attributable to Aboriginal people[4] and this is associated with high rates of ectopic pregnancy and infertility. Prescribers need to maintain a high index of suspicion and offer regionally appropriate empirical treatment according to the presentation. Routine screening for genital chlamydia among all young sexually active women is increasingly recommended by international authorities; for young Aboriginal women, this should be extended to include gonorrhoea tests. Asymptomatic men and women with risk factors should also be offered screening. Nucleic acid amplification tests have greatly simplified screening options (first-pass urine specimens for men and self-administered swabs or tampons for women). | Gonorrhoea treatment is informed by regional antibiotic sensitivity patterns. Amoxycillin is still first-line in the Northern Territory and Western Australia.<br>Azithromycin for chlamydia (single dose)<br>Benzathine penicillin for syphilis (single dose or weekly doses for three weeks depending on duration) |

Poisons legislation limits who is able to prescribe medicines. The formalisation of medicines training and reform of statutory law are important for Aboriginal health workers in defending their established clinical practices. Without such reforms, Aboriginal health workers risk being relegated to 'nurse assistant' roles.

The fact that prescribing activities are often outside the legal framework is a failure of health policy rather than a reflection on appropriate multidisciplinary practice. Legislative reform to cover such realities should not get caught up in territorial disputes between professional groups; the focus should be on how to ensure community access to and quality use of essential medicines.

In practice, withholding treatment is just not an option. In most remote settings, the caseload is heavy, the treatments are standard, the margin of safety for most of the commonly used drugs is high and there is often no doctor or pharmacist available. A failure to initiate therapy promptly in the Aboriginal health setting leads to serious adverse outcomes – such as rheumatic fever, cellulitis and septicaemia, complicated pneumonia, and amputation of diabetic feet.

## Ways forward

### *Access*

Improved mechanisms for supplying medicines to Aboriginal people are urgently required. A Commonwealth supply

arrangement for remote Aboriginal health services, under Section 100 provisions of the *National Health Act 1953*, was brokered through the Australian Pharmaceutical Advisory Council and implemented in 1998. Under the scheme, approved Aboriginal health services in remote areas can obtain bulk supplies of PBS-listed medicines from a community pharmacy, and can also access funding to provide professional pharmacist support services. This scheme has made a real difference in remote areas. Similar initiatives to improve access to medicines in rural and urban areas are an identified priority for the Commonwealth government and its Australian Pharmaceutical Advisory Council. Such reforms are eminently affordable: bringing Aboriginal access up to the level of the general community would represent a less than 1.5% increase in current PBS outlays.

### *Clinical practice guidelines and training*

What limited training that prescribers get in Aboriginal health has tended to be about history, cultural context, health determinants and barriers to care. While this is important, practitioners also need to be technically proficient in those areas where prescribing practice differs. The development of standard treatment manuals [8], and evidence-based resources that can support their development [4], continues to be an important strategy in supporting appropriate prescribing.

### *Statutory reform*

It is no longer tenable to have a medicines regulatory system that fails to provide a framework for established, responsible prescribing practice in remote areas. In an increasingly litigious environment, medical practitioners and health service providers are rightly concerned about medicolegal implications and insurers are reluctant to cover 'illegal dispensing'.

Without a statutory framework, health services may leave treatment decisions to the discretion of remote health staff as they feel unable to expressly condone an illegal practice. This leaves individual health workers exposed and unsupported. To ensure timely, safe and efficacious use of medicines in Aboriginal communities, the way forward must include statutory reform.

Ideally, a regionally customised standard treatment manual should serve as approved 'standing orders'. A problem-orientated standard treatment manual, incorporating clinical assessment and management decision points, provides a quality use of medicines framework for the use of prescription medicines by nurses and Aboriginal health workers in remote areas.

This approach is preferred over simply approving a drug formulary as it allows a link to be made between medicines and the particular clinical circumstances of use (including exceptions, referral and follow-up protocols). This also suits the context of multidisciplinary care, particularly where staff turnover is high.

The position of Aboriginal health workers who have existing clinical roles needs to be particularly safeguarded. Prescribing practice is tied up with broader issues of professional development, standards and training for Aboriginal health workers. Reforms should help empower communities to improve resources for their own health.

## Conclusions

The poor health status of the Aboriginal population and the lack of improvement over the last generation are particularly shameful in an international context. We know a great deal about the nature of the problems and how they should be addressed, yet commitment from governments to do more than incremental reform has been lacking. Improved access to medicines by Aboriginal communities is urgently required, as is legislative reform to support the role of Aboriginal health workers. Prescribers have an important role, not only in providing culturally safe, evidence-based health care appropriate to Aboriginal health problems and ensuring medicines supply, but in advocating for the health policy and service reforms that will make a real difference.

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*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 119)*

5. In Aboriginal people, suppurative skin infections are often related to scabies.
6. Amoxycillin is no longer recommended for acute otitis media in Aboriginal children.

# Book review

**Australian Medicines Handbook 2003**

**Adelaide: AMH; 2003. 749 pages.**

**Price: $152, students $99; CD-ROM $152; book and CD-ROM $202 (plus postage).**

*John Howie, Pharmacist, Orange, NSW*

The busy practitioner who needs an Australian reference for drugs available in this country does not want one which weighs several kilos or runs to two volumes – not as a first resort at any rate. The Australian Medicines Handbook, first published in 1998, is light and compact in size, yet comprehensive in content. Unlike other current texts the information is easy to read: the print is not too small or congested and is set in two columns (each 60 mm) to a page with bold black headings and blue sub-headings.

Each chapter represents an organ system or a broad therapeutic drug class within which drugs are grouped according to their indicated use and then introduced with information on rationale for use and considerations to be made before starting treatment. The action of each group is explained simply and clearly and indications and contraindications given. Special considerations such as coexisting medical conditions are dealt with and adverse effects listed according to whether they are common, infrequent or rare.

This latest edition includes new therapeutic topics covering acute coronary syndromes and androgenic alopecia. There is expanded information about vaccines as well as new evidence in many therapeutic areas, notably hormone replacement therapy, and the treatment and prevention of thromboembolism.

Perhaps the most useful information is to be found under the headings 'Comparative information' and 'Practice points'. The first of these will greatly assist the prescriber or reviewing pharmacist to decide which is the most appropriate drug within a class and this information is frequently set out in table form making it readily accessible. The second lists important points to be aware of when a drug is used (for example under Nitrates: 'tolerance to nitrates occurs with frequent or continuous exposure (may occur within 24 hours); avoid by ensuring a nitrate-free interval of 10–12 hours each day') and advice and information to give patients, an important consideration if medications are to be used effectively.

What I like most about this book is its clarity and brevity and the way important information is presented. It is impossible for example to miss the warning boxes inserted to emphasise a serious adverse effect. I cannot imagine anyone who is in need of a concise, accurate and up-to-date drug reference not wanting this volume as a primary reference and at $152 it is well worth the investment.

*Merilyn Liddell, Professor and Head, Department of General Practice, Monash University, Melbourne*

On first impression, the Australian Medicines Handbook (AMH) is attractive to look at and feel, and is small enough to keep easily to hand. I found the setting out good, although the soft mauve of the sub-headings is a little difficult to read, making it more difficult to find the section you are looking for. It is useful to have the numbers for the Poisons Information Centre and the Australian Sports Drug Agency inside the front cover in a prominent position.

The CD version is very easy to use, with an intuitive interface. It has menus which drop down at the point of the mouse, and an excellent search facility, with hot links. I had not used the CD version before, and found it better than expected. I would be interested to know if a PDA version is to be developed.*

The AMH maintains the very user-friendly general structure of the previous editions. It has 20 main chapters, based on body systems or a general therapeutic type. In each of these chapters it provides information about each particular class of drug (and some mention generally if there is or is not significant intraclass difference), followed by information about specific drugs in the class.

The great benefit of the AMH is its authoritative evidence-based content, independent of commercial interest. This is particularly important when needing information to choose between different drugs. Classic textbooks often stop at the class level, but the AMH includes authoritative discussion of intraclass difference. The amount of detail is well controlled – all the information is useful at a practical level, and the format allows quick scanning if just needing a specific piece of information. It is much easier to digest than formal product information material, and the content incorporates a wider range of evidence than included in product information.

Information on prescribing for particular groups is helpful, notably in pregnancy and lactation, children, the elderly, and in hepatic and renal insufficiency.

A couple of details that may be worth including in the future would be:

- information on sporting restrictions for particular drugs
- interactions between drugs and foods
- a full table of contents at the beginning of the hard copy.

These minor limitations however do not detract from it as being overall an excellent comprehensive and user-friendly text.

The AMH is in my view one of the absolutely key requirements for modern practice, especially for the general practitioner. It should have the same status as the stethoscope and the sphygmomanometer on the doctor's desk.

* *Editor's note:* A PDA version is planned.

DIAGNOSTIC TESTS

# Moving beyond sensitivity and specificity: using likelihood ratios to help interpret diagnostic tests

*John Attia, Senior Lecturer, Clinical Epidemiology, Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, Newcastle, New South Wales*


## SYNOPSIS

**Properties of diagnostic tests have traditionally been described using sensitivity, specificity, and positive and negative predictive values. These measures, however, reflect population characteristics and do not easily translate to individual patients. Likelihood ratios are a more practical way of making sense of diagnostic test results and have immediate clinical relevance. In general a useful test provides a high positive likelihood ratio and a small negative likelihood ratio.**


**Index words: abnormal laboratory results, sensitivity, specificity.**

*(Aust Prescr 2003;26:111–3)*

## Introduction

In clinical practice, physicians are often faced with interpreting the results of diagnostic tests. These results are not absolute. A negative test does not always rule out disease and some positive results can be false. As the prevalence of disease varies, the results of a test may have different implications; haematuria is more likely to be a sign of cancer in an elderly man than it is in a young woman.

## Sensitivity and specificity

Clinical epidemiology has long focused on sensitivity and specificity, as well as positive and negative predictive values, as a way of measuring the diagnostic utility of a test.[1] The test is compared against a reference ('gold') standard, and results are tabulated in a 2 x 2 table (Fig. 1). Sensitivity is the proportion of those with disease who test positive. Another way of saying this is that sensitivity is a measure of how well the test detects disease when it is really there; a sensitive test has few false negatives. Specificity is the proportion of those without disease who test negative. It measures how well the test rules out disease when it is really absent; a specific test has few false positives.

Although well established, sensitivity and specificity have some deficiencies in clinical use. This arises mainly from the fact that sensitivity and specificity are population measures, i.e. they summarise the characteristics of the test over a population.

How do we interpret results for an individual patient? What is the probability of disease in a 50-year-old male with suspected angina who has more than 1 mm of ST segment depression during an exercise stress test? What does a negative d-dimer test mean, in terms of the chance of having a deep vein thrombosis, for a 40-year-old female with a swollen calf? It is impossible for the clinician to know whether the positive result is a true positive or a false positive; or whether the negative result is a true negative or a false negative.

## Predictive values

What clinicians need is a measure that combines the true and false positives (or negatives) into one. The positive predictive value was such an attempt; it expresses the proportion of those with positive test results who truly have disease (Fig. 1). Another way of saying this is, given that a patient tests positive, what is the probability that they truly have disease? However, this measure is critically dependent on the population chosen and the prevalence of disease. The test performs less

*Fig. 1*

**Estimating the sensitivity and specificity of diagnostic tests[1]**

| | | True diagnosis 'gold standard' | | |
|---|---|---|---|---|
| | | Disease present | Disease absent | |
| Test results | Positive | a<br>True positive | b<br>False positive | a + b |
| | Negative | c<br>False negative | d<br>True negative | c + d |
| | | a + c | b + d | |

Sensitivity = a / (a + c)
Specificity = d / (b + d)

Positive predictive value = a / (a + b)
Negative predictive value = d / (c + d)

Positive likelihood ratio = $\frac{a / (a + c)}{b / (b + d)}$ Negative likelihood ratio = $\frac{c / (a + c)}{d / (b + d)}$

well the lower the prevalence. The same caveats are applicable to the negative predictive value. This means that the positive predictive value and negative predictive value are not transferable from one patient to another, or from one setting to another.

## Likelihood ratios

Likelihood ratios are independent of disease prevalence. They may be understood using the following analogy. Assume that a patient tests positive on a diagnostic test; if this were a perfect test, it would mean that the patient would certainly have the disease (true positive). The only thing that stops us from making this conclusion is that some patients without disease also test positive (false positive). We therefore have to correct the true positive (TP) rate by the false positive (FP) rate; this is done mathematically by dividing one by the other (Fig. 1).

Algebraically we can show that:

$$\text{Positive likelihood ratio} = \frac{\text{probability of positive test in those with disease}}{\text{probability of positive test in those without disease}}$$

$$= \text{TP rate} / \text{FP rate}$$
$$= (a/[a+c]) / (b/[b+d])$$
$$= \text{sensitivity} / (1 - \text{specificity})$$

Likewise, if a patient tests negative, we are still worried about the likelihood of this being a false negative (FN) rather than a true negative (TN). This likelihood is given mathematically by the probability of a negative test in those with disease, compared to the probability of a negative test in those without disease.

$$\text{Negative likelihood ratio} = \frac{\text{probability of negative test in those with disease}}{\text{probability of negative test in those without disease}}$$

$$= \text{FN rate} / \text{TN rate}$$
$$= (c/[a+c]) / (d/[b+d])$$
$$= (1 - \text{sensitivity}) / \text{specificity}$$

Likelihood ratios have a number of useful properties:

- because they are based on a **ratio** of sensitivity and specificity, they do not vary in different populations or settings
- they can be used directly at the individual patient level
- they allow the clinician to quantitate the probability of disease for any individual patient.

The interpretation of likelihood ratios is intuitive: the larger the positive likelihood ratio, the greater the likelihood of disease; the smaller the negative likelihood ratio, the lesser the likelihood of disease.

To see how likelihood ratios work, let us take the example of the 50-year-old male with the positive stress test. It is known that a more than 1 mm depression on exercise stress testing has a sensitivity and specificity of 65% and 89% respectively for coronary artery disease when compared to the reference standard of angiography.[2] This means that:

$$\text{Positive likelihood ratio} = 0.65 / (1 - 0.89) = 5.9$$

The **likelihood** of this patient having disease has increased by approximately six-fold given the positive test result. To translate this into a **probability** of disease one must use Bayes' Theorem.*

Bayes' Theorem states that the pre-test **odds** of disease multiplied by the likelihood ratio yields the post-test **odds** of disease. Note that because of the theorem's mathematical properties, the likelihood ratios must be used with **odds** rather than per cent probability of disease. To avoid the bother of converting fractions to odds, multiplying by the odds ratio, getting the post-test odds and converting back to a fraction, the Bayes' nomogram is used (Fig. 2).[3] In this nomogram, the pre-test probability is located on the first axis, and joined to the likelihood ratio, on the second axis, to read off the post-test probability on the third axis.

For example, if we estimate from our clinical assessment that the 50-year-old male has a 40% chance of having coronary artery disease, we join 40% on the first axis with 6 on the second axis and read off the post-test probability of 80%, i.e. the patient has an 80% chance of having coronary artery disease given the positive test result.

Likewise, let us estimate that the 40-year-old woman has a 17% chance of having a deep vein thrombosis. A d-dimer test has a sensitivity of 89% and a specificity of 77%. This means that:

$$\text{Negative likelihood ratio} = (1 - 0.89) / 0.77 = 0.14$$

Using Bayes' nomogram, and joining 17% with 0.14, we read off a post-test probability of approximately 3%. This means that after a negative test the woman has a 3% chance of having a deep vein thrombosis.

It is important to note that likelihood ratios always refer to the likelihood of having disease; the positive and negative designation simply refers to the test result. Hence the interpretation of the post-test odds is always a likelihood of having disease.

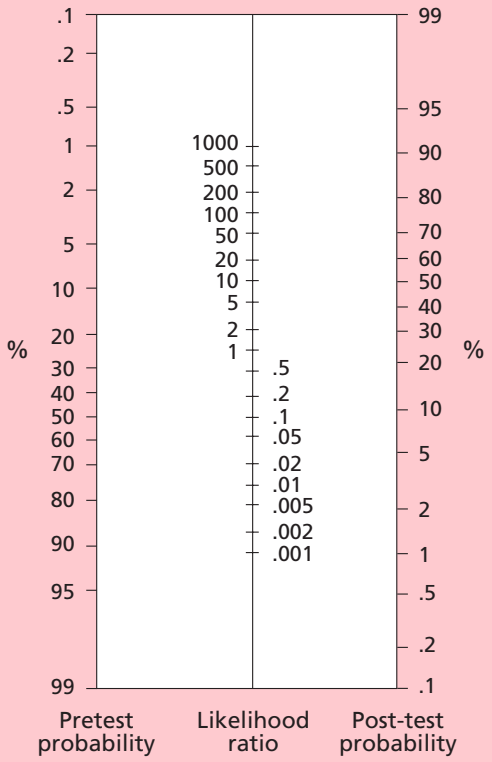
These scenarios highlight some additional advantages of using likelihood ratios. They enable the clinician to talk quantitatively about the risk of disease which may allow more informed decision making on the part of the patient. Likelihood ratios emphasise the reality that we are never 100% sure of the diagnosis. Rather than looking at diagnostic tests as a yes or no answer to the question of whether a patient has disease, it makes us realise that positive or negative results simply increase or decrease the likelihood of disease, judged on the basis of our history and physical examination. Various items of the history and examination can be seen as diagnostic tests, and can have likelihood ratios associated with them.

Although likelihood ratios are clinically very useful, a significant barrier to using them in routine practice is the amount of time required to do literature searching, in order to identify the sensitivity and specificity of the tests. Fortunately, as their use is increasing, authors have compiled likelihood ratios for common tests.[4,5]

*Fig. 2*

**Bayes' nomogram**

Pre-test probability is located on the first axis and joined to the appropriate likelihood ratio on the second axis. The post-test probability is then read off the third axis.




## Pre-test probability

The Bayes' nomogram requires an estimation of the probability of disease. There are two methods of estimating the pre-test probability:

- the most frequent method is simply to use one's clinical experience and to attach a number to one's 'gut feeling' after the history and examination
- clinical decision rules.

Clinical decision rules have been published for a small number of clinical problems. For example, based on three questions regarding the quality of chest pain, clinicians can estimate the pre-test probability of coronary artery disease.[2] Likewise, various signs and symptoms can be given a point score to arrive at a pre-test probability of deep vein thrombosis[6] (Table 1). Unfortunately, such decision rules are rare, and difficult to find, although they have recently been compiled in a book.[7]

## Conclusion

Likelihood ratios are a useful and practical way of expressing the power of diagnostic tests in increasing or decreasing the likelihood of disease. Unlike sensitivity and specificity, which are population characteristics, likelihood ratios can be used at the individual patient level. Using likelihood ratios and Bayes' nomogram allows us to convert a pre-test probability, based on an educated guess or a clinical decision rule, to a post-test probability.

*Table 1*

**Clinical decision rule for deep vein thrombosis**

| *Clinical feature* | *Score* |
|---|---|
| Active cancer | 1 |
| Paralysis, paresis or recent plaster | 1 |
| Bedridden for more than three days or major surgery within four weeks | 1 |
| Localised tenderness | 1 |
| Entire leg swollen | 1 |
| Calf swelling more than 3 cm | 1 |
| Pitting oedema | 1 |
| Collateral superficial veins | 1 |
| Alternative diagnosis as likely as or greater than that of deep vein thrombosis | -2 |

A score is given for the presence of certain clinical features. The total score reflects the probability of having a deep vein thrombosis.

≤ 0 is low probability (3%)
1–2 is moderate (17%)
≥ 3 is high (75%)

* Bayes' Theorem is available electronically at various evidence-based medicine web sites, e.g.

http://www.cebm.net/nomogram.asp (for nomogram)

http://www.health.usyd.edu.au/resources/ebm/bayestxt.htm (for calculator)

http://pdacentral.ozbytes.net.au/palm/calculators_medical_default.html (see EBM calculator, to download to a Palm Pilot)

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# Managing drug-induced hyponatraemia in adults

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## SYNOPSIS

**Drug-induced hyponatraemia is commonly associated with diuretics, selective serotonin reuptake inhibitors and antiepileptics. With increasing polypharmacy and an ageing population, the prevalence of drug-induced hyponatraemia is likely to increase. Most patients with drug-induced hyponatraemia are asymptomatic and the diagnosis is made incidentally following routine blood tests. Mild cases may be managed either by stopping the drug or by careful observation if the drug is considered essential. More severe hyponatraemia may require fluid restriction in the short term as well as withdrawal of the causal drug. Referral may be required for patients with acute illness and for those with severe and/or refractory hyponatraemia.**

**Index words: adverse effects, diuretics, antidepressant drugs, sodium.**

*(Aust Prescr 2003;26:114–7)*

## Introduction

Hyponatraemia is defined as a serum sodium concentration below 135 mmol/L. It occurs commonly and is often discovered on a routine blood test. A Melbourne laboratory found hyponatraemia in 4.8% of 326 923 samples from ambulatory patients and 14% of 84 464 samples from admitted patients referred by general practitioners. In these patients, serum sodium was less than 115 mmol/L in 0.3%, 115–124 mmol/L in 4% and 125–135 mmol/L in 96% (L. Eilermann, Melbourne Pathology, personal communication 2002).

Although drugs are a common cause of hyponatraemia, other causes should be considered (Table 1).[1] Assessing the patient's fluid status and plasma osmolality can help in finding the cause. As hyponatraemia is often associated with fluid retention (dilutional hyponatraemia) the osmolality is usually reduced, however other causes may be associated with normal or increased osmolality.

In normovolaemic patients the syndrome of inappropriate secretion of antidiuretic hormone is the most frequent mechanism for hyponatraemia. Drugs are often responsible for this syndrome, but may cause hyponatraemia in other ways (Table 2). In Australia, drug-related hyponatraemia is most commonly reported in association with diuretics and selective serotonin reuptake inhibitors (SSRIs), but other drugs can be implicated (Table 3).

With mild drug-related hyponatraemia the drug should be stopped where possible, but if the drug is essential continue it

*Table 1*

**Causes of hyponatraemia ***

**Hypotonic hyponatraemia**

***Reduced water excretion***

*Increased extracellular fluid volume*

congestive cardiac failure, cirrhosis, nephrotic syndrome, renal failure

*Normal extracellular fluid volume*

- thiazide diuretics
- hypothyroidism, adrenal insufficiency
- syndrome of inappropriate secretion of antidiuretic hormone
  - many drugs (see Table 2)
  - cancers
  - disorders of the central nervous system
  - pulmonary disorders
  - severe nausea and/or pain
- decreased salt intake

*Decreased extracellular fluid volume*

- renal sodium loss e.g. diuretics, osmotic diuresis, adrenal insufficiency, salt-wasting nephropathy
- extra-renal sodium loss e.g. diarrhoea, vomiting, sweating, fluid sequestration in 'third space' in surgical patients

***Excess water intake***

- primary polydypsia
- low sodium irrigations or infusions during procedures
- tap water enemas
- dilute infant formulae

**Isotonic hyponatraemia**

- pseudohyponatraemia associated with severe hyperglycaemia, hypertriglyceridaemia and hyperproteinaemia
- spurious hyponatraemia in blood taken proximal to dextrose infusions

**Hypertonic**

- increased extracellular, non-permeable solute e.g. glucose, hypertonic mannitol

* adapted from reference 1

*Table 2*

**Probable mechanisms of drug-induced hyponatraemia**

| *Class* | *Mechanism* |
|---|---|
| Diuretic | decreases total body sodium |
| SSRI and MAOI | SIADH |
| Anticonvulsant carbamazepine | SIADH |
| ACE inhibitor | SIADH ? |
| NSAID | SIADH |
| Hormone analogues desmopressin (DDAVP) oxytocin | exogenous antidiuretic hormone |

SSRI selective serotonin reuptake inhibitor
MAOI monoamine oxidase inhibitor
SIADH syndrome of inappropriate secretion of antidiuretic hormone
ACE angiotensin converting enzyme
NSAID non-steroidal anti-inflammatory drug

while monitoring the hyponatraemia. When hyponatraemia is more marked short-term fluid restriction and medication withdrawal may be required. In other circumstances (Table 4) referral is advisable.

## Assessment

The management of a patient with hyponatraemia depends on their clinical status and the likelihood that one or more drugs are responsible. Assessment and management should consider the following:

- hyponatraemia is often found in healthy and/or asymptomatic people
- most hyponatraemic patients have no symptoms or signs of hyponatraemia
- although neurological symptoms like restlessness, confusion, seizures and drowsiness, can result from hyponatraemia, there may be alternative explanations, even in patients with alarmingly low serum sodium concentrations
- alternative explanations for hyponatraemia including cardiac, liver or renal failure should be considered
- a latent tendency for hyponatraemia may only become apparent when fluid intake is increased, e.g. when fluids are 'pushed' after admission to hospital
- serum sodium measurements, or a battery of tests including sodium, may be specifically requested for sound clinical reasons, or included in tests primarily undertaken for other reasons.

The history and examination will often establish the cause of hyponatraemia, but measuring plasma osmolality can sometimes help in the differential diagnosis.

Diagnostic and therapeutic issues are illustrated in the following case studies.

*Table 3*

**Drugs commonly associated with hyponatraemia**

| *Class* | *Drug* | *Number of reports ** |
|---|---|---|
| Diuretic | | |
| thiazide | indapamide | 180 |
| | chlorothiazide | 16 |
| combination | amiloride/hydrochlorothiazide | 116 |
| loop | frusemide | 62 |
| Antidepressant | | |
| SSRI | sertraline | 130 |
| | fluoxetine | 50 |
| | paroxetine | 46 |
| | citalopram | 35 |
| | venlafaxine | 49 |
| MAOI | moclobemide | 19 |
| Antipsychotic | clozapine | 14 |
| Anticonvulsant | carbamazepine | 101 |
| ACE inhibitor | enalapril | 21 |
| | captopril | 12 |
| ACE inhibitor/diuretic | perindopril/indapamide | 18 |
| COX-2 inhibitor | celecoxib | 24 |
| Hypnotic | temazepam | 13 |
| Chemotherapeutic | vincristine, vinblastine, carboplatin, cisplatin, cyclophosphamide | 25 |
| Sulfonylurea | glipizide, glimepiride, glibenclamide, gliclazide | |
| Hormone analogue | desmopressin (DDAVP), oxytocin | |
| Proton pump inhibitor | omeprazole, pantoprazole | |
| Recreational | 3,4 MDMA ('ecstacy')[4] | |

* Numbers are given when there were more than 10 spontaneous reports to the Australian Adverse Drug Reactions Advisory Committee 1972–2002. These numbers do not give the rate of adverse drug reactions.

SSRI selective serotonin reuptake inhibitor
MAOI monoamine oxidase inhibitor
ACE angiotensin converting enzyme
COX cyclo-oxygenase
MDMA 3,4-methylenedioxymethamphetamine

*Table 4*

**Hyponatraemia: clinical features to raise concern**

Acute illness

Neurological symptoms – increasing confusion, decreasing conscious state, seizures

Dehydration – postural hypotension, tachycardia, oliguria

Fluid overload related to comorbid chronic disease – cardiac, renal or liver disease

Worsening hyponatraemia or failure to respond to treatment

Severe hyponatraemia – (Na+ < 120 mmol/L)

## Case 1: Incidental hyponatraemia

You request 'serum creatinine and electrolytes' after deciding to check the renal function of a woman 77 years of age who has proteinuria on 'dipstick' testing. She feels and looks well, has no new symptoms, but has type 2 diabetes, osteoporosis, depression and hypertension. Her medications are alendronate, gliclazide, aspirin, perindopril and amlodipine. She started paroxetine 18 months ago for a relapse of depression.

Serum creatinine is normal, but sodium is 127 mmol/L. According to your records, serum sodium was within normal limits two years ago.

***What is the differential diagnosis?***

- drug-induced hyponatraemia – paroxetine, perindopril
- 'pseudohyponatraemia' resulting from hyperglycaemia
- dehydration
- occult comorbidities
  - endocrine – hypothyroidism, hypoadrenalism
  - syndrome of inappropriate secretion of antidiuretic hormone e.g. malignancy, central nervous system lesion
  - cardiac, renal or liver disease. These are unlikely if she is otherwise well.

***What is the most likely cause?***

The most likely cause is the SSRI paroxetine. The prevalence of significant hyponatraemia has not been determined from large prospective studies, but a retrospective Australian study showed that the risk is 5.6 times higher in elderly psychiatric inpatients taking SSRIs or venlafaxine than in controls.[2] Hyponatraemia is more likely in older patients and in those taking other drugs associated with hyponatraemia, such as diuretics. In such patients serum sodium should be checked before and several weeks after starting an SSRI.[2]

***How would you manage this patient?***

A careful history and examination are needed to exclude non-drug causes of hyponatraemia. In an elderly patient like this, the possibility of dehydration and hypothyroidism should be considered. Blood glucose measurement is required to exclude pseudohyponatraemia.

Glucose expands the plasma volume creating an additional sodium-free space. Blood glucose concentrations above 20 mmol/L can therefore spuriously reduce the serum sodium concentration measured by flame photometry. Treatment of the hyperglycaemia should return the sodium concentration to normal. Marked hypertriglyceridaemia and hyperproteinaemia can also cause pseudohyponatraemia in the same way as hyperglycaemia.

Once pseudohyponatraemia has been excluded the most likely cause is paroxetine, which could be continued, as the serum sodium is not dangerously low. Measurement of serum and urine osmolality and urinary sodium might support the diagnosis of inappropriate secretion of antidiuretic hormone related to the SSRI, but these additional tests are not essential here.

The patient should be advised not to drink fluids for purely 'social' reasons. Her serum sodium could be re-checked in a week. If her serum sodium falls further, or if she becomes unwell, the SSRI should be ceased and alternative therapy for depression sought. If a non-drug cause of inappropriate antidiuretic hormone secretion is considered likely following a full clinical reassessment and medication withdrawal, a chest X-ray, to exclude a pulmonary cause, or cerebral computerised tomography, seeking a space-occupying lesion, might be requested.

## Case 2: Monitoring for hyponatraemia

A 65-year-old smoker has hypertension, hyperlipidaemia, ischaemic heart disease and congestive cardiac failure. He takes lisinopril, frusemide, indapamide, aspirin, simvastatin and carvedilol. He is feeling well, but you request serum creatinine and electrolytes. His potassium, creatinine and blood glucose are normal, but his sodium is 122 mmol/L.

***What is the differential diagnosis?***

- drug-induced hyponatraemia – indapamide, frusemide, lisinopril
- cardiac failure – fluid overload
- 'pseudohyponatraemia' – resulting from hypertriglyceridaemia
- occult comorbidities
  - liver or renal disease
  - endocrine – hypothyroidism, hypoadrenalism
  - syndrome of inappropriate secretion of antidiuretic hormone e.g. malignancy, central nervous system lesion.

***What is the most likely cause of his hyponatraemia?***

A careful history and examination should focus on the possibilities of both fluid overload and of reduced extracellular fluid (see box opposite). Measure standing and lying blood pressure, pulse rate and jugular venous pressure, and check for peripheral oedema and crackles in the lung bases. If you are satisfied the patient is normovolaemic and there is no clinical suspicion of alternative causes you could assume the hyponatraemia is drug-induced. Although the most likely drug in this case is indapamide[3], frusemide or lisinopril could be responsible or contributory.

***How would you manage the patient?***

Indapamide should be ceased and gentle fluid restriction and daily weighing is recommended. Electrolytes should be monitored with the expectation that the serum sodium concentration should improve within a week. Alternative treatment may be required for hypertension and heart failure. Should hyponatraemia persist, you may need to consider a trial of withholding frusemide. Tests of serum and urine osmolality and urinary sodium are difficult to interpret in the context of diuretic use and the results will not contribute to the patient's management.

## Case 3: Acutely unwell with hyponatraemia

A woman 32 years of age has epilepsy which is well-controlled by carbamazepine. She has been unwell with increasing lethargy and a 10 kg weight loss in three months. For the last three days

she has been nauseated and has vomited twice. She looks unwell, is slightly pigmented and has postural hypotension. Serum sodium is 120 mmol/L and serum potassium and creatinine are slightly increased.

***What is the differential diagnosis?***

- adrenal insufficiency
- drug-induced hyponatraemia – carbamazepine
- occult comorbidities
  - endocrine e.g. hypothyroidism
  - cardiac, liver or renal disease
  - syndrome of inappropriate secretion of antidiuretic hormone e.g. malignancy, central nervous system lesion.

***What is the most likely cause?***

The most likely cause is adrenal insufficiency given that the woman has hyperpigmentation and mild hyperkalaemia. Although carbamazepine is a recognised cause of hyponatraemia, it is an unlikely cause of hyponatraemia in this patient as the clinical features are so suggestive of adrenal insufficiency.

***How would you manage the patient?***

The acute management of this patient includes establishing intravenous access, giving 100 mg hydrocortisone and rehydrating her with intravenous normal saline. Other important acute measures include lying the patient supine and arranging for her admission.

Urgent referral to hospital should be considered for all patients with acute illness and significant hyponatraemia. The decision to refer other patients with hyponatraemia for urgent investigation and treatment is based on the key clinical features outlined in Table 4. Such patients may require fluid restriction, saline infusion and close monitoring. In patients with severe hyponatraemia it is especially important not to correct hyponatraemia too quickly, as the osmotic effects may cause irreversible neurological complications, specifically central pontine myelinolysis.

**Assessing fluid status**

Features of reduced extracellular fluid:

- dry mucous membranes
- tachycardia
- postural hypotension
- oliguria
- increased urine specific gravity
- increased serum urea and creatinine

Features of fluid overload:

- elevated jugular venous pressure
- tachycardia
- tachypnoea
- added heart sounds
- crackles in the lung bases
- oedema


## Summary

Drug-induced hyponatraemia occurs in approximately 5% of outpatients and 15% of inpatients. In Australia from 1972 to 2002, the commonest drugs causing hyponatraemia were indapamide, sertraline, amiloride/hydrochlorothiazide, carbamazepine, frusemide and fluoxetine. Most patients with hyponatraemia are diagnosed incidentally on routine blood tests. Non-drug causes of hyponatraemia should always be considered. In the majority of patients hyponatraemia is mild. These patients are asymptomatic and do not require any specific therapy. In severe cases urgent treatment and referral are necessary.


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*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 119)*

7. The syndrome of inappropriate secretion of antidiuretic hormone is usually due to a pituitary tumour.
8. Hyperglycaemia can cause pseudohyponatraemia.

# 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 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.

## Aripiprazole

Abilify (Bristol-Myers Squibb)

10 mg, 15 mg, 20 mg and 30 mg tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2.2

Aripiprazole is a new atypical antipsychotic. These drugs are less likely to cause extrapyramidal adverse effects than typical antipsychotics such as haloperidol.

As aripiprazole is a partial agonist at dopamine ($D_2$) receptors it may increase neurotransmission if the concentration of dopamine is low and decrease neurotransmission if the dopamine concentration is high. This action may have effects on the positive and negative symptoms of schizophrenia. Aripiprazole is also a partial agonist at serotonin ($5HT_{1A}$) receptors, but an antagonist of $5HT_{2A}$ receptors.

The drug only needs to be taken once a day. After absorption, aripiprazole is converted to an active metabolite. As aripiprazole and its metabolite have long half-lives steady-state plasma concentrations are not reached for approximately two weeks. Dose increases should therefore be at least two weeks apart.

The metabolism of aripiprazole involves cytochrome P450 2D6 and 3A4. This increases the potential for interactions with drugs such as fluoxetine, paroxetine and carbamazepine. Most of the unchanged drug and its metabolites are excreted in the faeces.

The clinical trials of aripiprazole have used rating scales such as the Positive and Negative Syndrome Scale (PANSS) to assess the drug's efficacy. In most short-term studies (4–6 weeks) aripiprazole has had a greater effect than placebo on this scale. One of the trials included haloperidol as an active control. Although haloperidol and aripiprazole reduced the PANSS scores significantly more than placebo, the study was not designed to show a difference between the active treatments.[1]

In clinical trials common adverse events included headache, nausea, anxiety and insomnia. Compared to haloperidol, aripiprazole caused less somnolence and extrapyramidal effects, but more nausea and dizziness.[1] As aripiprazole acts as an antagonist at $\alpha_1$ adrenergic receptors it may cause orthostatic hypotension, so it should be used cautiously in patients with cardiovascular disease. Patients may gain weight during long-term treatment. As with other antipsychotics, aripiprazole has been reported to cause neuroleptic malignant syndrome.

Although aripiprazole appears to have little effect on prolactin secretion or the QT interval of the ECG, it is unclear if it has significant clinical advantages. Despite being approved for maintenance treatment there is little published information about the long-term safety and efficacy of aripiprazole. It needs to be compared with other atypical antipsychotics in long-term trials to establish its place in therapy.

REFERENCE*

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

## Memantine

Ebixa (Lundbeck)

10 mg tablets

50 mL bottles containing 10 mg/mL oral solution

Approved indication: Alzheimer's disease

Australian Medicines Handbook section 16.4

The currently available drug treatments for Alzheimer's disease are donepezil, galantamine, rivastigmine and tacrine. These drugs inhibit acetylcholinesterase so cholinergic adverse effects can be a problem. Memantine aims to improve the patient's function by a different mechanism – antagonism at the N-methyl-D-aspartate (NMDA) receptors.

The NMDA receptor is one of the receptors for glutamate, a cerebral neurotransmitter. If neuronal dysfunction in dementia is related to increased concentrations of glutamate, then blocking the receptors could slow progression of the disease.

In a clinical trial 252 patients, with moderate or severe Alzheimer's disease, were randomised to take memantine or a placebo for 28 weeks. Although 71 patients did not complete the trial, those given memantine showed less decline on some of the rating scales used to assess efficacy. These patients' scores were significantly different from placebo on the Alzheimer's Disease Co-operative Study Activities of Daily Living Inventory (ADCS-ADL), the Severe Impairment Battery (SIB) and the Functional Assessment Staging scale (FAST). There was also a significant difference in the clinicians' and carers' assessments of the patients.[1]

Many patients in the trial had adverse events including agitation, urinary incontinence, diarrhoea and insomnia.[1] Adverse effects with a higher frequency than placebo include fatigue, headache, dizziness and hallucinations. Approximately 11% of patients will stop treatment because of adverse effects.

To reduce the risk of adverse effects memantine should be started at a low dose and slowly increased over a month. The drug is completely absorbed even if taken with food. Most of the dose is excreted unchanged in the urine, so a lower dose is needed if renal function is reduced. There are potential

interactions with drugs such as cimetidine which use the same renal transport system. Memantine may also interact with antipsychotics, levodopa and other dopaminergic drugs.

Although memantine may have an advantage over placebo, it is important to remember that, on average, all the patients in the clinical trial got worse. There was also no significant difference between memantine and placebo in some of the assessments such as the Mini-Mental State Examination, the Global Deterioration Scale and the Neuropsychiatric Inventory. In addition the results can be influenced by how the data from the 28% of patients who dropped out are analysed. A different analysis negates the significant differences in the clinicians' impressions of change.[1]

Although the options for the treatment of moderate to severe dementia are limited, memantine does not seem to be a major advance. (It has been available in Germany for approximately 20 years.) Further research is exploring whether treating patients with a combination of memantine and an acetylcholinesterase inhibitor will be of greater clinical benefit.

REFERENCE†

1. Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

## NEW FORMULATIONS

### Desmopressin acetate

Minirin (Ferring)

200 microgram tablets

### Follitropin alfa

Gonal-F (Serono)

75 IU, 450 IU and 1050 IU powder for injection

### Oestradiol

Aerodiol (Servier)

150 microgram per actuation nasal spray

### Progesterone

Crinone 8% (Serono)

90 mg/1.125 g vaginal gel tube

## Answers to self-test questions

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

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