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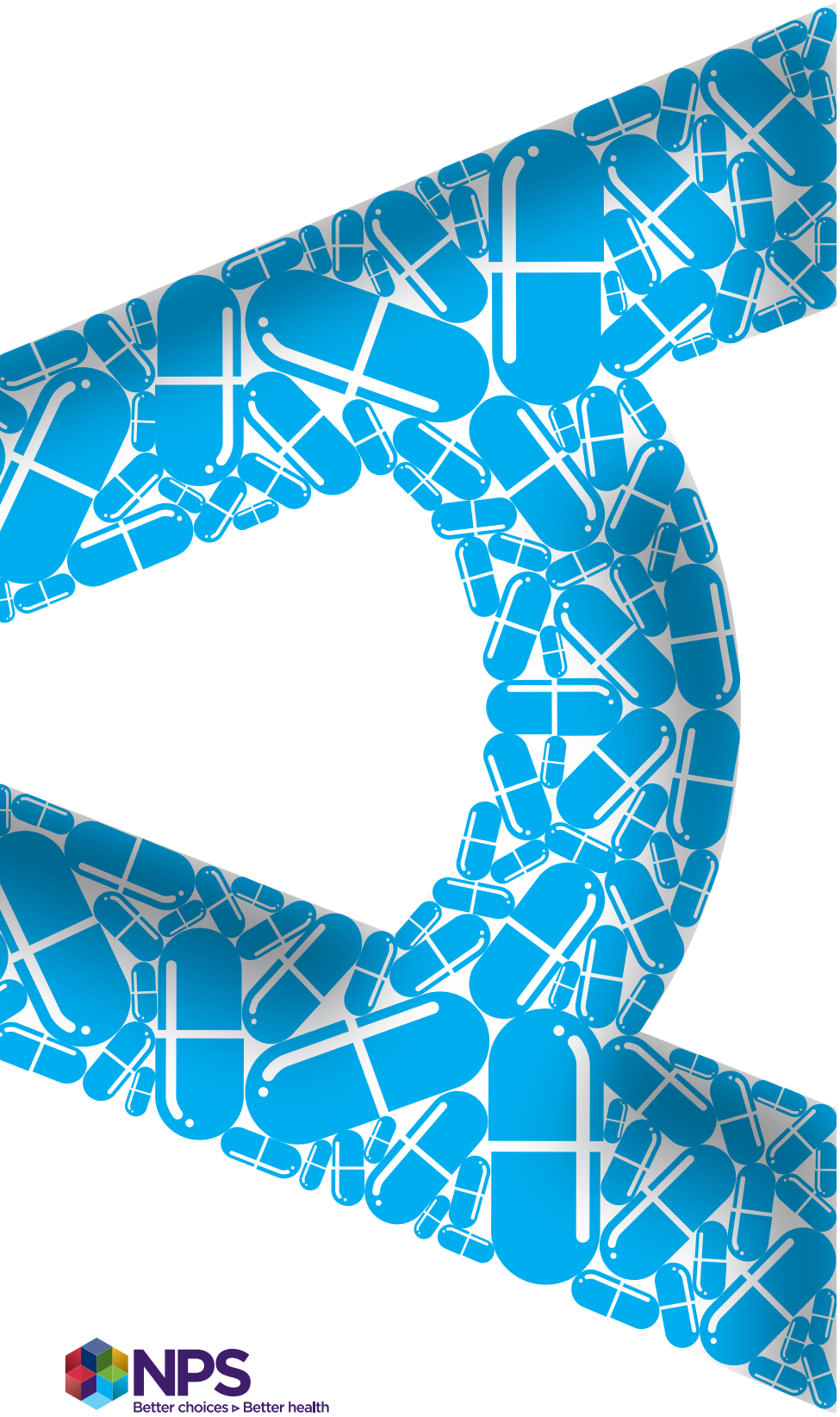

NPS Better choices ▸ Better health

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Deferring PBAC decisions: rationing as a reality

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Key words
cost of drugs, National Medicines Policy

Aust Prescr 2012;35:2–3

At first glance, a decision not to implement a recommendation by the Pharmaceutical Benefits Advisory Committee (PBAC) to list a drug on the Pharmaceutical Benefits Scheme (PBS) seems ridiculous. The Australian PBS has a worldwide reputation for its rigorous cost-effectiveness analyses. What could be the logic for not listing a drug that has been judged to be cost effective? There are several issues to consider.

First, we should recognise that a new drug is judged to be cost effective based on calculations from appropriate clinical trials. These calculations must show that the overall price to be paid (that is, the cost) for one person to live a year longer (adjusted for quality of life) compares favourably with that calculated for other drugs that are already listed on the PBS.

However, such an analysis tells us nothing about how spending money on the drug compares with other possible uses of the money. More lives might be saved, for instance, by spending the money on other areas of the health budget, such as employing more nurses, or even outside the health budget, such as building bicycle paths. In an ideal world, other possible uses of the money would be subjected to cost-effectiveness analyses equal in rigour to those for new drugs. However, the data needed for such analyses are never likely to be available, so judgements must be based on other criteria. This immediately raises the difficult question of what those other criteria should be. However, the difficulty of the question should not mean that we automatically put it in the 'too hard basket'.

Second, we should recognise that the listing of a new drug on the PBS can lead to an increased overall cost to government – in some cases a major increase – despite the drug being assessed as cost effective. For example, the marketing skills of the pharmaceutical industry will often lead to a rapid increase in the overall use of a drug class when there is a new addition to the class, even though the new drug is of equal cost effectiveness to existing drugs within that class. 'Leakage' of indications, where the drug is prescribed for indications other than those on which the cost-effectiveness analysis was based, can also lead to much greater costs without necessarily achieving additional benefits.

Third, even if the drug is cost effective, the cost commences immediately, but the benefits often only accrue in later years. Apart from the practical issue of finding the extra money upfront, this raises the equity issue of today's taxpayers paying for future taxpayers' benefits.

The PBS, for all its virtues, is not perfect. I would argue, for example, that costs will inevitably continue to rise while the PBS is driven by submissions from pharmaceutical companies wanting their products to be subsidised by the public purse. The industry is extremely good at 'playing the game' and tightly controls the design and publication of the trials that generate the data used in cost-effectiveness calculations. It is also expert at marketing its products and creating increased demand (and thus costs), whether or not a true need exists for new products.

From the Editor

Welcome to the new look *Australian Prescriber*. The first issue of the new design is filled with interesting information.

We begin with Rob Moulds and Brendan Shaw giving their opinions on the decision to defer the inclusion of some new drugs on the Pharmaceutical Benefits Scheme.

The Pharmaceutical Benefits Scheme also provides doctors with a range of drugs for use in an emergency. A table of suggested doses appears in this issue, but are some of the drugs still appropriate for practice in the 21st century? John Holmes assesses the emergency drugs and proposes some changes to the contents of the doctor's bag.

Opioids are not only used in emergencies, but are also prescribed for chronic pain. As there has been an increased use of opioids for non-cancer pain, Michael McDonough advises on how to reduce the dangers of this treatment.

Dangerous drugs need not be prescription medicines. Medicines Safety Update warns us about the hazards of some of the products available from the internet. Patients may not mention that they are using a product such as a complementary medicine. Margaret Duguid reminds us to ask patients about all the medicines they are taking. This is an important part of the process of medication reconciliation which aims to reduce medication errors.

Benjamin Davies is also concerned about drugs and other substances available online. Some substances can be difficult to detect in the laboratory.

Laboratory testing has a role in identifying the cause of fever in travellers. However, Anthony Gherardin and Jennifer Sisson emphasise the continuing importance of a thorough history and examination.

EDITORIAL

We have become accustomed to a healthcare system where only the best will do, regardless of the cost. My experience of working for many years in a country with far fewer resources than Australia has taught me that good use of older and cheaper drugs can achieve excellent clinical results. Is it really so unreasonable to be asked to use drugs that are 'almost as good' for a bit longer, rather than expect immediate access to every new drug that is assessed to be cost effective?

A positive aspect of the current debate is that it has resulted in a window, albeit brief and probably inadvertently created, during which we can reconsider the whole function of the PBS – which was created to ensure the public had access to new and expensive drugs to treat life-threatening conditions. The PBS continues to be a pillar of the National Medicines Policy, which states 'cost should not constitute a substantial barrier to people's access to medicines they need'.[1]

Is it time to return to basics and start with the conditions that need to be treated, rather than the drugs for which the pharmaceutical industry is seeking subsidy? Shouldn't we learn from developing countries where guidelines for therapy drive essential drug lists rather than the other way around? Rigorous cost-effectiveness analysis will always be an essential tool in guiding the allocation of public money to the PBS. However, it makes more sense for those analyses to aid the development of guidelines for treating the conditions affecting Australians rather than using them as the sole determinant for adding a new drug to the PBS, which is in practice Australia's essential drugs list.

Good use of older and cheaper drugs can achieve excellent clinical results

Rob Moulds is the Medical advisor to Therapeutic Guidelines Ltd, an independent not-for-profit company that publishes clinical practice guidelines for use in Australian healthcare institutions and general practices.

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Deferring PBAC decisions: industry view

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Key words
cost of drugs, drug industry

Aust Prescr 2012;35:3–4

The Australian Government's decision in February 2011 to defer the listing of seven medicines and one vaccine on the Pharmaceutical Benefits Scheme (PBS) has been one of the most widely deplored health policies in recent memory. The decision appeared to ignore the advice of the government's own independent, expert advisory committee, the Pharmaceutical Benefits Advisory Committee (PBAC). It was condemned by the innovative and generic medicines industries, and also by patient groups, the medical profession, the broader community and academia. There were also motions in both houses of Parliament and a Senate inquiry.[1] Out of 65 submissions to the Senate inquiry, the only one to support the government's position was that of the Department of Health and Ageing.

It was in the wake of that inquiry that the Prime Minister announced, on 30 September 2011, that the six remaining deferred medicines (paliperidone palmitate, oxycodone/naloxone, budesonide with eformoterol, botulinum toxin type A, dalteparin sodium and nafarelin) would be listed on the PBS on 1 December 2011. The other two products (dutasteride and pneumococcal conjugate vaccine) had been listed on 1 September 2011. This was a welcome breakthrough to an impasse that had lasted more than seven months.

These listings were particularly good news for the patients who had been waiting for additional affordable treatments for conditions such as severe axillary hyperhidrosis, schizophrenia and chronic pain. In an agreement co-signed by Medicines Australia, the Consumers Health Forum, the Generic Medicines Industry Association and the Australian Government, the signatories committed to continue negotiations to seek a satisfactory solution. The government also agreed that for a period of 12 months no more medicines that cost under $10 million a year would be deferred while the negotiations continued.

The announcement fell well short of resolving the issue. It was a case of two steps forward, one step back and raised more questions than it answered. The agreement to accept PBAC advice on medicines under $10 million is a temporary measure which gives little long-term confidence that the government is committed to reversing its policy permanently.

EDITORIAL

Deferring PBAC decisions: industry view

On the very same day as the Prime Minister's announcement, another drug, dabigatran, was sent for further review. This was despite a recommendation by the PBAC that the drug be listed on the PBS. Again this has caused significant uncertainty for the companies that supply medicines to the PBS.

For companies submitting medicines for PBS listing, the decision generated enormous uncertainty

Cabinet taking an increasingly interventionist approach to the listing of medicines on the PBS raises a number of questions and concerns for patients as well as the companies that supply the PBS. It is unclear what criteria were used by Cabinet to select which medicines would be listed and which would not.

For the pharmaceutical companies submitting medicines for listing on the PBS, the decision generated enormous uncertainty. After the announcement in February 2011, a number of companies indicated that they would suspend their applications for listing new medicines on the PBS due to the ongoing uncertainty. Eleven out of 26 companies, or around 42%, responding to a Medicines Australia member survey conducted in 2011 indicated that they were considering delaying submissions of new medicines for the PBS because of the government's decision to defer the listing of some medicines.[2] Politicians making decisions about which medicines to list on the PBS effectively adds a new, higher hurdle in the listing process that companies cannot plan for.

For patients, the decisions to defer medicines denied them subsidised access to additional treatment options. While the government argued at the time that there were alternatives available, it became increasingly clear that the deferred medicines provided additional treatment options that were valued by patients and doctors.

The government openly acknowledged that the reason it deferred these medicines and vaccines was not through any lack of efficacy in the medicines themselves, but because of its concerns about its own financial situation. However, the Department of Health and Ageing's own 2011 annual report[3] shows that for 2010–11, expenditure on the PBS grew at 5.7% in nominal terms. Taking into account that inflation grew over the same period at 3.6% suggests that the PBS is growing at around 2% in real terms. This is more or less equal to the government's target for all expenditure growth.

The government's own Intergenerational Report projects that the PBS as a proportion of gross domestic product will be flat until 2020.[4] This means that the government's own projections show that the PBS will not be growing faster than the economy out to 2020. So whatever concerns the government has about broader health expenditure, the PBS is one area that is being well contained. For a major healthcare program to have such minimal growth, while still providing access to the latest medicines to a growing and ageing population, is an extraordinary achievement.

By denying Australians subsidised access to new medicines that have been assessed by experts to be clinically and cost effective, we run the real risk that we will end up with a two-tier health system. High-income patients can afford the most effective and convenient treatment options, while the rest will have to make do with less convenient treatments already on the PBS.

Australia should not be a country where we cannot afford to provide medicines for sick people. Providing industry with some level of predictability improves their ability to provide medicines to Australians through the PBS.

Dr Shaw is Chief executive of Medicines Australia, the industry association representing Australia's innovative medicines industry.

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Letters to the Editor

Securing the supply chain

Editor, – Thank you for Elizabeth de Somer's clear article explaining the complexities involved in the supply chain of medicines (Aust Prescr 2011;34:105-7).

From a prescriber's perspective, we are well informed when a medicine is discontinued, but temporary lack of supply is rarely advertised. Too often, we find out when a patient returns with an unfilled script. Similarly when supply returns to normal, prescribers are often the last to know.

It would be helpful to have access to a list of unavailable items, including at least the more common drugs. With the almost universal use of electronic prescribing, a simple alert of a supply problem could easily be incorporated into prescribing software.

Could Medicines Australia perhaps facilitate this process with the relevant software developers?

Andrew Montanari
General practitioner
Newcastle

Elizabeth de Somer, author of the article, comments:

Medicines Australia is the peak body representing manufacturers of prescription medicines that are involved in the research and development of new medicines (www.medicinesaustralia.com.au).

Unfortunately, Medicines Australia would not be able to facilitate building an alert system into prescribing or dispensing software. The manufacturer is also unable to control or monitor the stock levels held by individual pharmacies.

When a product is listed on the Pharmaceutical Benefits Scheme, supply is a condition of listing. Any advance knowledge of expected supply interruptions or shortages to PBS listed items will therefore be communicated to the Pharmaceutical Benefits Division of the Department of Health and Ageing, and the Therapeutic Goods Administration. Strategies for managing supply will be agreed, and these include sponsors alerting healthcare professionals to the issue and providing advice on any agreed management approach.

Prescribers may not be made aware of short-term supply chain difficulties occurring at the pharmacy. It is also likely that the manufacturer would be unaware of these types of stock outages. With 5000 community pharmacies across Australia, local supply shortages can occur in individual pharmacies unrelated to any action by the manufacturer, and may be caused by wholesaler and pharmacy ordering, stock decisions or unexpected spikes in local demand.

The Australian Government is progressing the development of electronic health records management with the aim of maximising electronic data linkages.[1]

The Pharmacy Guild of Australia is the national peak body for community pharmacy and liaises with governments and software providers to develop pharmacy tools that meet the needs of the community.[2]

The NPS recently conducted a review that identified the most important features of prescribing software that impact patient safety.[3] This was supported by the Medical Software Industry Association.[4]

The impact of short-term stock outages related to individual pharmacy supplies may be a significant problem for prescribers to track and may require some consideration by these groups.

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Pharmaceutical excipients

Editor, – The authors of the article 'Pharmaceutical excipients – where do we begin?' (Aust Prescr 2011;34:112-4) make a very important point regarding the role of excipients in medications. Nowhere is this more relevant than in the treatment of epilepsy.

This concept has major ramifications for the use of generic drugs, but most recently we came across a series of patients who actually had significantly elevated blood concentrations of lamotrigine while remaining on the parent compound.[1] Our initial worry was that these patients had been changed to a generic, but review of medication excluded that. Nothing in the way of measurement of their concentrations had changed. The pharmaceutical company producing the parent compound confirmed

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

LETTERS

that they had sourced their product from a different manufacturing site. Consequently, the only plausible interpretation of the altered concentrations is that the excipient was altered, resulting in patients having altered bioavailability and hence marked increases in lamotrigine concentrations. Some patients experienced considerable toxicity.

The role of the excipient should not be underestimated and there is good reason to follow blood concentrations, particularly of antiepileptic medications, in patients who may be swapped from parent compound to generic. However, even the parent compound may equate to the equivalent of a generic if sourced from a different manufacturing site with possible different excipient.

Roy G Beran
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Vinflunine

Editor, – It was with interest that we read your opinion on vinflunine in the new drugs section of *Australian Prescriber* (2011;34:122). It is important however to also provide the information which formed the basis of the positive assessment of vinflunine's benefit–risk balance by the Therapeutic Goods Administration (TGA).

Vinflunine is the only drug registered for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a platinum-containing regimen. It received marketing approval from the TGA in 2011 and the European Medicines Agency in 2009.

Vinflunine's benefit is described as modest in your article. The TGA's clinical evaluator assessed the benefit of vinflunine as significant and meaningful over a range of efficacy parameters: response rate, disease control rates, progression free survival and overall survival.[1] A statistically significant 2.6 month increase in overall survival observed in the eligible population, which most closely reflects the population intended for treatment (6.9 months versus 4.3 months in the control arm)[2], is clinically meaningful in a rapidly progressing disease and similar to that of docetaxel, the standard treatment in castration-resistant metastatic prostate cancer (+ 2.4 months).[3]

The TGA concluded that vinflunine's safety profile was well characterised, acceptable and manageable by appropriate dose modifications leading to a low rate of discontinuation and treatment-related deaths.[1] Further, that vinflunine is generally well tolerated by patients. The main dose limiting toxicity associated with vinflunine is neutropenia but, as pointed out by the TGA, neutropenia is a familiar adverse event that oncologists are used to managing by a variety of medical measures.[1] Your opinion of myelosuppression as being a considerable problem with vinflunine and describing vinflunine's adverse effects as severe is not a fair assessment of the adverse effect profile of this drug.

Your concluding quote that 'it is better to focus on individually tailored palliative care' is taken from a single French drug bulletin[4] as opposed to numerous peer-reviewed oncology journals which conclude the contrary.[5-9] The conclusion of the TGA's clinical evaluator, that the vinflunine data support a positive benefit–risk balance for its approved indication in patients who have few available therapeutic options, is more reliable.[1]

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ARTICLE

Time to restock the doctor's bag

SUMMARY

The Pharmaceutical Benefits Scheme provides emergency drugs for the doctor's bag.

Most of the drugs are for injection into patients with acute medical or psychiatric problems. However, it is not appropriate to give some of these drugs without critical care support.

In some situations an injection is not the preferred route of administration.

Several of the drugs are not best practice. It is therefore time to review the contents of the doctor's bag.

Introduction

There are relatively few conditions that mandate the administration of emergency drugs outside hospital. However, there will be occasions when a general practitioner may be required to give emergency drugs. Such cases include patients with status epilepticus, cardiac arrest, acute severe asthma, anaphylaxis, acute severe pain or when there is a suspicion of sepsis, especially meningococcal disease.

For many years the Pharmaceutical Benefits Scheme has provided general practitioners with emergency (doctor's bag) drugs. However, there has been little substantive review of the scheme. Some of the drugs currently available no longer represent best practice and should be replaced. Consideration should also be given to withdrawing some drugs from the scheme on the grounds of lack of efficacy, necessity or safety.

All medical practitioners should know about the dosage and administration of emergency drugs and should be equipped and prepared to manage adverse events that may arise from their use. Important potential adverse effects include hypotension, cardiac arrhythmias, altered level of consciousness, upper and lower airway obstruction, respiratory depression and convulsions.

Most parenteral emergency drugs should be administered intravenously and if possible an intravenous infusion of normal saline or Hartmann's solution should be established before their administration. Occasionally the oral route is preferable, such as an oral benzodiazepine for acute anxiety states or oral olanzapine in acute agitation.

Drugs that should be replaced

Some drugs are no longer first-line in the treatment of emergencies. They should be replaced or supplemented with better alternatives.

Benzylpenicillin

The early administration of antibiotics can be lifesaving in overwhelming sepsis. In particular, meningococcaemia may result in extremely rapid deterioration and suspected cases must be treated urgently. Benzylpenicillin is still recommended as a first-line treatment before the patient gets to hospital, but there is increasing antibiotic resistance. Around 70% of meningococcal isolates in Australia show decreased susceptibility to penicillins,[1] but high doses of benzylpenicillin may overcome some of the antibiotic resistance.

Ceftriaxone or cefotaxime (intramuscularly or intravenously) may be better options as currently all Australian meningococcal isolates remain sensitive to these cephalosporins.[1] With a broad spectrum of antibacterial activity, they are also indicated in severe undifferentiated sepsis of any cause.

A small proportion of patients with hypersensitivity to penicillin may also have an anaphylactoid response to cephalosporins. When confronted with likely meningococcal disease, the risks of treatment need to be weighed against the imperative of early antibiotic treatment. In patients with known penicillin hypersensitivity, ceftriaxone or cefotaxime should be given in preference to benzylpenicillin but the practitioner must be prepared to resuscitate with adrenaline and intravenous fluids in the event of a major anaphylactoid reaction.[2]

Diazepam

Benzodiazepines are indicated in status epilepticus and severe agitation. The parenteral form of diazepam is highly irritant to veins and has unpredictable bioavailability when administered intramuscularly. Rectal diazepam is rarely used. Midazolam is an alternative to diazepam in both adults and children. Unlike diazepam, midazolam can be administered either intramuscularly or intravenously with more predictable effects. As with all sedating drugs, the practitioner must be able to recognise and treat adverse effects including hypotension and compromised airway and breathing which can be fatal.

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Key words
emergency drugs, Pharmaceutical Benefits Scheme

Aust Prescr 2012;35:7–9

Haloperidol and chlorpromazine

Haloperidol is useful in the management of an acutely agitated or psychotic patient, but may cause severe extrapyramidal adverse effects, prolonged sedation and cardiac arrhythmias due to prolongation of the QTc interval. Chlorpromazine may cause significant hypotension.

Olanzapine (5–10 mg orally or intramuscularly) may be a better option for behavioural disturbance in psychosis.[3] It has fewer adverse effects than haloperidol, but large doses of olanzapine may cause cardiorespiratory collapse. Antipsychotics and benzodiazepines should not be given within one hour of each other. In long-term use of olanzapine there is an increased risk of stroke and death in patients with dementia.

Frusemide

The traditional role of frusemide in the management of acute ventricular failure is now uncertain. In acute pulmonary oedema, first-line therapy is preload reduction with nitrates such as glyceryl trinitrate either sublingually or (preferably) by intravenous infusion, and non-invasive ventilation with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP). The diuretic action of frusemide may not be as important as reducing cardiac preload, and vascular depletion may be deleterious especially in right ventricular failure. Frusemide may also raise plasma renin and noradrenaline levels, exacerbating afterload and increasing myocardial oxygen demand, thereby aggravating coronary ischaemia.[4,5]

For the present it is reasonable to continue to recommend the use of intravenous boluses of frusemide in acute left ventricular failure as second- or third-line treatment.

Drugs have no first-line role in cardiac arrest outside hospital

Drugs that should be withdrawn or restricted

Some drugs should be withdrawn from the doctor's bag because they are relatively ineffective, inappropriate or unsafe. Many drugs are potentially more dangerous than beneficial and a medical emergency is not the time for a practitioner to be giving an unfamiliar drug.

Antiarrhythmics – lignocaine and verapamil

Drugs have no first-line role in cardiac arrest outside hospital where the highest priority is basic life support, in particular effective chest compressions. Electrical defibrillation should be administered as soon as possible when cardiac arrest is due to ventricular fibrillation or pulseless ventricular tachycardia.[6]

The management of acute cardiac dysrhythmias requires specific training and experience. Attempts at cardioversion should be made only in hospital unless a patient is critically haemodynamically compromised.

Amiodarone or sotalol are now preferred over lignocaine in the treatment of ventricular tachyarrhythmias, but may do more harm than good if the patient is otherwise stable. Similarly adenosine has largely superseded verapamil for the treatment of atrioventricular nodal re-entry tachycardia (the commonest cause of paroxysmal supraventricular tachyarrhythmia) but has potential adverse effects including bronchospasm.

As with ventricular arrhythmias, it is dangerous to treat supraventricular tachyarrhythmias in an uncontrolled environment. The diagnosis may not be straightforward and verapamil may be inappropriate for some supraventricular dysrhythmias. For example in Wolff-Parkinson-White syndrome, blocking the atrioventricular node with verapamil may lead to unopposed conduction down the accessory pathway and precipitate ventricular tachycardia, or even ventricular fibrillation. Verapamil is also a negative inotrope and can exacerbate hypotension especially if cardioversion has failed.

It follows that any attempt at pharmacological cardioversion should only be attempted with full resuscitation facilities and ongoing cardiovascular monitoring. There is no necessity for any antiarrhythmic to be available in the doctor's bag for use outside hospital.

As a general rule, patients with acute dysrhythmias should be transferred to hospital. No immediate treatment is required if they are haemodynamically stable. Drug therapy is contraindicated if the patient is haemodynamically compromised in which case the safest treatment is direct current cardioversion.

Procaine penicillin

There is no emergency indication to justify the continued use of this outdated formulation.

Terbutaline injection

Acute severe asthma is initially treated with inhaled bronchodilators, systemic corticosteroids and oxygen when indicated. Current asthma guidelines do not recommend the use of parenteral beta agonists.[7,8] Systematic reviews show that these drugs offer little if any benefit and have been associated with worse outcomes, probably due to increased ventilation-perfusion mismatching.[8] Intravenous beta agonists also cause hypokalaemia and adverse cardiovascular effects.

Tramadol

Tramadol is less effective than morphine and offers no advantage in the treatment of acute pain. Unless the patient has a proven allergy, morphine is the drug of choice and can safely be used for all causes of severe pain not controlled by oral analgesia including ureteric and biliary colic. Morphine can be given subcutaneously, intramuscularly or intravenously. Repeated small doses titrated until the patient is comfortable minimise the risk of respiratory depression.

Morphine may cause histamine release, but true anaphylaxis is very rare. Tramadol, however, has been associated with life-threatening angioneurotic oedema. It also has potentially serious interactions with commonly used drugs, especially selective serotonin reuptake inhibitors with which it can precipitate a serotonergic syndrome.

Conclusion

The emergency drug supply system is a valuable resource for general practitioners. The best outcomes occur when the patients are expeditiously transported to a hospital. In time-critical cases, however, a general practitioner may be required to respond urgently to an acutely ill patient. It is essential that the drugs in the doctor's bag should reflect current best emergency practice, efficacy and safety. With these principles in mind, the current doctor's bag emergency drug scheme should be reviewed. ◁

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FURTHER READING

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Cover story

Australian Prescriber has been published by the NPS since 2002. In 2010 the National Prescribing Service changed its name to NPS: Better choices, Better health, and decided to rebrand all its publications. As the previous design of *Australian Prescriber* first appeared in 2004, there was also a need for an update.

Health professionals and students participated in the research for the new design of *Australian Prescriber*. Their comments have helped to create a layout which will make it easy for readers to find all the information which interests them.

In addition to the summary of each article, key points and self-test questions will be highlighted. There is more white space in the design to aid readability, particularly for busy health professionals.

Since 2010 *Australian Prescriber* has used paper certified by the Forest Stewardship Council. The new stock also comes from responsible sources.

Our new design includes not only the NPS brand, but also elements from the history of *Australian Prescriber*. The capsules on the cover recall the first design of the journal in 1975. Although it is in a stylised form, the eye of Horus from 1994 is still there, looking to the future of medicine and *Australian Prescriber*.

DIAGNOSTIC TESTS

Assessing fever in the returned traveller

Anthony Gherardin
National medical adviser
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SUMMARY

There are many causes of fever after travel, ranging from common and self-limiting to serious and life-threatening.

Priorities for management are to identify conditions that are life-threatening, treatable, or have public health implications.

Common diagnoses are malaria and dengue fever, respiratory illness and diarrhoeal illness.

Malaria is important to exclude in any febrile person who has travelled or lived in a malaria transmission area.

Careful assessment of travellers with fever involves a detailed history, a thorough examination and targeted laboratory investigations.

Patients with undifferentiated fever should be referred to an infectious disease physician.

Introduction

It is estimated that febrile illness (temperature greater than 38° C) occurs in about 2–3% of travellers, and accounts for about a quarter of post-travel presentations for medical care.[1] Fever after travel may be due to a wide spectrum of causes, many of which are minor and self-limiting, but could include serious, rapidly-progressive or potentially fatal causes. The severity of illness varies widely also, with presentations of patients with fever ranging from mild inconvenience to patients requiring urgent hospital admission. While most travel-related infections present within a few months of return, some infections can present many months or years after exposure, such as strongyloides or schistosomiasis.[2]

Causes such as malaria or meningococcal disease are treatable with early recognition and specific management. Infectious causes may be of public health concern, and require specific intervention to prevent spread. The management of post-travel fever should therefore be directed at identifying treatable causes, especially for potentially fatal or rapidly-progressive disease, and managing any potential for communicable spread.[3]

Laboratory testing is important in establishing a proper diagnosis, including drug sensitivity where relevant. Many exotic or tropical illnesses may present similarly or non-specifically, yet establishing the exact diagnosis and circumstances of infection can be important to both the patient and others. Overdiagnosis in the field is common. In a Tanzanian study, most febrile travellers were empirically diagnosed and treated for malaria.[4] Another study showed that many febrile travellers in Asia were labelled and treated for typhoid fever.[5] This may lead to incorrect labelling of 'treatment failure' and associated avoidable morbidity.

Causes

Common causes of travel-related fever include malaria, influenza, dengue fever, rickettsial infections, non-specific viral syndromes and bacterial diarrhoea.[6-9] Febrile illness, such as common infections, malignancy and autoimmune disorders, may be unrelated to travel. Fever may also have a non-infectious cause related to travel such as pulmonary emboli or drug reactions.

Infectious causes of fever after travel could have been acquired before, en route or even after the specific travel, so care with history-taking is important. Specific causes of fever vary depending on the patient's destination.[6] The largest study of unwell returned travellers, the GeoSentinel database, showed the following causes of fever in returned travellers:[7]

- systemic febrile illness – 35% (malaria, dengue, typhoid, rickettsia)
- unspecified febrile illness – 22%
- acute diarrhoea – 15%
- respiratory illness – 14% (pneumonia, bronchitis, sinusitis)
- vaccine-preventable illness – 3% (hepatitis A and B, typhoid).

While fever without local symptoms is common, it may be more difficult to diagnose than fever associated with localising syndromes. Common presentations with fever include a rash, jaundice, abdominal pain or eosinophilia.[1,8]

Assessing the patient

A thorough history and examination of the patient should be the first step to making a diagnosis. A useful guide to the evaluation and initial management of fever in a returned traveller is shown in Fig. 1.[2]

Patient history

The history should include the following:

- the medical history of the patient including age, past surgeries, drugs, allergies, vaccines, immune status (HIV, diabetes, pregnancy)
- a detailed account of the travel history, including destinations, activities and possible exposures (see Table 1), timeframes of travel, season at destination
- a detailed sequential history of the current illness, associated symptoms or signs, concurrent therapies, and whether other people have been affected. Information about the pattern of fever may be sought, although this is often not useful because of the use of antipyretics and antibiotics.

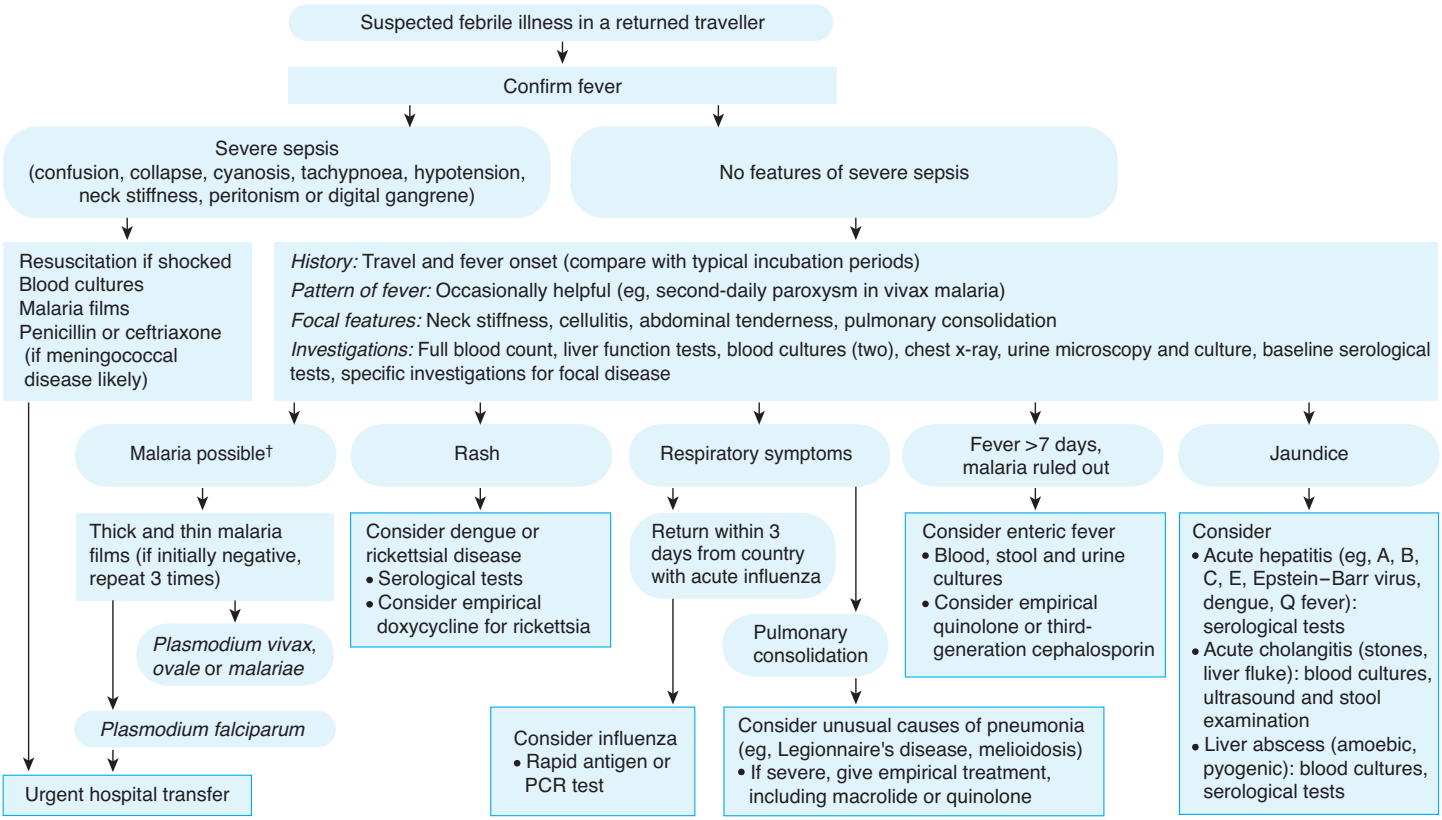
A checklist for history-taking in returned travellers is shown in Table 2.

It is important to identify if a traveller is a first or second generation emigrant traveller going back to visit friends and relatives, as these people have been shown to be at higher risk of travel-related morbidity.[9] This is because they have increased exposures to pathogens and decreased rate of preventative behaviours, such as vaccinations, before they travel.

Physical examination

Physical examination should include all systems. Important clinical features to look for include lymphadenopathy, hepatomegaly, splenomegaly, jaundice, anaemia, wheeze, rash or skin lesions, muscle or joint involvement, neck stiffness, photophobia, conjunctivitis, neurological signs or evidence of bleeding. Urine should be examined by dipstick initially for blood and glucose. Repeated examination may be required to monitor the evolution of symptoms and signs, and response to therapy.

Fig. 1 **Evaluation and initial management of fever in a returned traveller***



PCR polymerase chain reaction

* Evaluation should also include the differential diagnoses that would be considered in a non-traveller with fever

† Travel to high-risk area, rural or prolonged travel, non-compliance with prophylaxis

From: Looke DFM and Robson JMB. 9: Infections in the returned traveller. MJA 2002;177:212-219. ©Copyright 2002. *The Medical Journal of Australia* – reproduced with permission.

Table 1 **Particular exposures and possible infections**

EXPOSURE	DISEASE
Drinking unclean water	Viral diarrhoea, shigella, salmonella, hepatitis A and E, giardia, polio, cryptosporidium, Guinea-worm
Skin contact in unclean water	Leptospirosis, schistosomiasis, free-living amoeba
Eating raw or improperly cooked food	Food-borne viruses and bacteria, wide range of parasites, brucellosis, listeriosis
Animal bites	Rabies, rat-bite fever, wound infections, simian herpes B-virus, cat-scratch fever
Animal contact	Q-fever, anthrax, toxoplasma, Hanta viruses, Nipah/Hendra viruses, severe acute respiratory syndrome, plague
Bird contact	Psittacosis, avian influenza
Mosquito bites	Malaria, dengue, yellow fever, arboviruses, viral encephalitis, filariasis
Tick bites	Rickettsia, borrelia, tick-born encephalitis, Q-fever, Crimean-Congo haemorrhagic fever, tularaemia, babesiosis
Fly bites	African trypanosomiasis, onchocerciasis, leishmaniasis, loa loa, sandfly fever, bartonella
Flea bites	Plague, murine typhus, tungiasis
Lice bites	Relapsing fever, epidemic typhus, trench fever
Mite bites	Scrub typhus, rickettsial pox
Triatomine bug bite	Chagas disease
Soil-skin contact	Hookworm, strongyloides, melioidosis, fungal infections, mycobacteria
Sexual contact	HIV, hepatitis A, B and C, sexually transmitted diseases
Injections, body-piercing	Hepatitis B and C, HIV, malaria, mycobacteria, leishmaniasis

Table 2 **Checklist for taking a history in returned travellers**

QUESTIONS	EXAMPLES
Country of origin and country of travel	Latent disease, possible exposures
Occupation, hobbies, activities	Farmer, abattoir worker, cave explorer
Prophylaxis	Immunisations, malaria prophylaxis, insect repellents
Treatments or procedures	Blood transfusions, injections, splenectomy, gastrectomy, tattoos
Drugs	Prescribed, over-the-counter, illicit
Diet	Seafood, raw food, traditional or homemade food
Sex	Unprotected sex, HIV partner, multiple partners, commercial sex
Allergies	Antibiotics, food, insect bites, plant
Bites	Insects, snake, animal, spider, human
Pets	Birds, dogs, cats, other
Family history	Diabetes, sickle-cell anaemia, tuberculosis

Clues to finding the cause of fever

The findings of the history and examination are then considered against the geographical distribution of infectious diseases and their incubation periods. Knowing the incubation period of certain diseases can assist in making the diagnosis, and while the exact date of exposure may not be determined, the departure and return dates may define the possible range of incubation periods, helping to rule in or out certain diagnoses (Table 3). For instance, an incubation period of less than two weeks rules out diseases such as amoebic liver disease, viral hepatitis, filariasis, visceral leishmaniasis and tuberculosis, whereas an incubation period beyond three weeks rules out dengue, rickettsia, haemorrhagic fevers and most bacterial infections including leptospirosis. Malaria can present from two weeks and up to months after return. Most cases (90%) of *Plasmodium falciparum* present within one month of return, whereas half of *P. vivax* cases present after one month.[2]

The presence of significant immune suppression also alters the possible range of infectious diseases as opportunistic infections must be considered. Other key physical findings may suggest certain diagnostic possibilities (Table 4). Remote travel within Australia also presents some risk of unusual communicable diseases (Table 5).

Laboratory tests

Initial screening of an undifferentiated fever should include:

- full blood examination with differential count and platelet count
- liver function tests
- thick and thin blood smears for malaria (could be supplemented by rapid tests where available)
- blood culture
- urinanalysis (infection, bilirubin)
- chest X-ray if patient is unwell.

Consider collecting an extra serum specimen to be held at the laboratory for future serology.

Routine screening may also help identify causes of potentially severe diseases such as malaria and typhoid. In addition to routine screening, extra investigations may need to be performed based on findings from the history and examination.[10]

Specific testing may be suggested by the clinical presentation, and guidance should be sought for the most appropriate specimen for the particular disease or phase of the disease.

Malarial smears

When malaria smears are ordered, it is preferable to refer to a recognised reference laboratory to minimise the chance of a false negative reading, as the experience of the technician is important. If malaria is suspected and the initial smear is negative, smears may need to be repeated at 24-hour intervals or sooner in severe disease. Negative smears can be due to low parasitaemia or can occur despite a high load with *P. falciparum* due to sequestration. Malaria should always be reconsidered if a traveller has returned from an area where transmission occurs, regardless of whether they took chemoprophylaxis,[11] or whether they are afebrile at the time of assessment.

Blood cell counts

The full blood examination and platelet count can be very helpful. Notably normal or low white cell counts occur in many infections including dengue, chikungunya, malaria, rickettsia and typhoid. Thrombocytopenia is seen in malaria, viral infections (especially viral haemorrhagic fevers including dengue) and in severe sepsis. Polymorphonuclear lymphocytosis usually reflects a bacterial infection, which could include leptospirosis or relapsing fever, but more often is due to common pyogenic organisms. Eosinophilia suggests invasive parasitic infection such as Katayama fever in schistosomiasis, or the migratory phase of some helminths or strongyloides. It also occurs in drug reactions and some fungal infections. Normal concentrations of non-specific markers such as C-reactive protein do not exclude serious illness.[1]

Other tests

Newer technologies like polymerase chain reaction-based tests may offer rapid and specific diagnosis, such as in dengue infection, but may also have a limited window to be positive. In general, positive bacterial specimens should be subjected to antibiotic sensitivity testing to guide therapy.

Referral and admission

When there is no clear diagnosis, patients should be referred to an infectious disease physician or major hospital for management. If the history and examination suggest a particular cause, patients can be managed outside hospital as long as there is access to diagnostics and prompt clinical review. Common conditions such as influenza or diarrhoea can generally be managed at home, but indications for referral for any illness should include suspected malaria, atypical presentations, or worsening clinical condition, in particular with onset of shock,

Table 3 **Average incubation periods for selected diseases**

INCUBATION PERIOD	DISEASES
Short (<10 days)	Arboviruses including dengue, chikungunya, bacillary dysentery, influenza, legionella, meningococcal, Marburg/Lassa fevers, plague, relapsing fever, rickettsial spotted fevers, scrub typhus
Intermediate (10–21 days)	African trypanosomiasis, brucellosis, hepatitis A and E, leptospirosis, malaria, typhoid, polio, epidemic typhus, Q-fever
Long (>21 days)	Hepatitis B, malaria, amoebic liver disease, visceral leishmaniasis, melioidosis, rabies, tuberculosis, filariasis, HIV, schistosomiasis

Table 4 **Key physical findings suggestive of cause of fever**

CLINICAL FINDING	POSSIBLE DIAGNOSES
Rash, maculopapular	Dengue, rickettsia, acute HIV, typhoid, scarlet fever, gonococcal, syphilis
Rash, petechial	Rickettsia, meningococcal, viral haemorrhagic fevers, leptospirosis
Eschars	Scrub typhus, tick-bite fever, anthrax, spider bites
Ulcers	Leishmaniasis, mycobacteria, anthrax
Jaundice	Hepatitis, malaria, leptospirosis, relapsing fever
Lymphadenopathy	Leishmaniasis, plague, rickettsia, brucellosis, toxoplasmosis, HIV, Lassa fever
Hepatomegaly	Malaria, leishmaniasis, schistosomiasis, liver abscess, typhoid, hepatitis, leptospirosis
Splenomegaly	Malaria, leishmaniasis, relapsing fever, trypanosomiasis, typhus, dengue, schistosomiasis, brucellosis

Table 5 **Unusual diseases present in Australia**

EXPOSURE	DISEASES
Mosquito	Alphaviruses – Ross River virus, Barmah Forest virus Flaviviruses – Murray Valley encephalitis, Kunjin virus, dengue, Japanese encephalitis
Tick	Queensland tick typhus, Flinders Island spotted fever
Mite	Scrub typhus
Soil and water	Melioidosis, leptospirosis
Animal	Australian bat lyssavirus, Hendra virus, Q-fever, brucellosis
Various	Mycobacteria – Bairnsdale ulcer, tuberculosis, leprosy, avian complex, trachoma

neurological, haemorrhagic or acute respiratory symptoms. Cases of poor response to treatment, persistent fever (fever for greater than seven days), or other chronic symptoms (greater than three weeks) should also be referred for specialist management.

Public health responses in Australia

Australia has 65 communicable diseases requiring notification by clinicians to state public health authorities. Many of these are diseases likely to be acquired through travel. Cumulative incidence is available through Communicable Diseases Intelligence reporting by the Australian Government Department of Health and Ageing.[12]

Quarantinable diseases, of which Australia currently has eight, include cholera, highly pathogenic avian influenza (H5N1), plague, rabies, severe acute respiratory syndrome (SARS), smallpox, the viral haemorrhagic fevers and yellow fever. Fortunately these are unlikely causes of fever in Australian travellers, although cholera and rabies have both caused recent outbreaks in tourist destinations. Quarantinable diseases are listed because they demand a major public health response.

The 2009 H1N1 pandemic highlighted the need to take a travel history when evaluating a patient with an undifferentiated influenza-like illness, and the requirement for an appropriate public health response.

Conclusion

Common diagnoses of fever in returned travellers are malaria, dengue fever, respiratory illness and diarrhoeal illness. Malaria is important to exclude in any febrile person who has travelled or lived in a malaria transmission area. Careful assessment of travellers with fever involves a detailed history, a thorough examination and targeted laboratory investigations. Patients should be referred to an infectious disease physician when a clear diagnosis is not made. <

Conflict of interest: none declared

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ARTICLE

The importance of medication reconciliation for patients and practitioners

SUMMARY

Medication errors are common and often occur when patients move between healthcare settings.

Around half of hospital medication errors occur on admission, transfer and discharge. Around 30% of these have the potential to cause patient harm.

Advanced age and taking several prescription medicines are associated with an increased risk of medication errors on admission.

At least one in six patients may have a clinically significant medication discrepancy on transfer within a hospital. Discrepancies also often occur at discharge and may cause problems in general practice.

The process of medication reconciliation can significantly decrease errors. It involves obtaining, verifying and documenting a list of the patient's current medicines and comparing this list to the medication orders and the patient's condition to identify and resolve any discrepancies.

Medication reconciliation is an important element of patient safety.

Introduction

A common patient safety problem around the world is the lack of accurate and complete information about patients' medicines when their care is transferred between healthcare settings. In up to two-thirds of patients there are variances between the medicines they take at home and the medicines ordered on admission to hospital.[1] It has been estimated that around half of the medication errors that happen in hospital occur on admission or discharge from a clinical unit or hospital.[2] Around 30% of these errors have the potential to cause patient harm.[3,4] These errors are also an economic burden to health services.[5]

The problem is not confined to hospital. Patients may have several specialist prescribers as well as their general practitioner. If there is not good communication between all the prescribers there is potential for medication errors. Studies in ambulatory care settings report 26–87% of medication records as incomplete or having discrepancies between medicines taken by the patient and those documented in the patient record.[6] In an Australian study only 58% of general practitioners' referrals to a specialist contained the correct dosage and number of prescribed medicines. Complementary and over-the-counter medicines were documented in 26% of letters.[7]

Causes of medication errors at interfaces of care

Errors can occur:

- on admission when determining the medicines the patient is currently taking
- when recording details of the patient's medicines in the medical record
- when prescribing medicines for the patient after admission, on transfer to another ward and at discharge.[5]

Drug history on admission

Drug histories are often incomplete with strengths, dose and drug forms missing (see case 1) and non-prescribed medicines, such as over-the-counter or complementary medicines, often omitted. Studies have shown that 10–67% of medication histories contain at least one error.[1]

In hospital the history is used to inform the inpatient medication orders, to make treatment decisions and to identify adverse medicines events. If errors are not corrected they continue throughout the patient's stay. Incomplete medication histories at the time of admission have been cited as the cause of at least 27% of prescribing errors.[8] The most common error is the omission of a regularly used medicine.[4,9,10]

Erroneous drug histories can lead to discontinuity of therapy, recommencement of ceased medicines, inappropriate therapy and failure to detect a drug-related problem. These errors can have adverse consequences for the patient during their hospital stay. Perpetuation of these errors on discharge may result in adverse events, from duplication of therapy, drug interactions and discontinuation of an essential medicine (see case 2).

Recording medicines on admission

The current processes for recording drug histories have been described as inadequate, potentially

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dangerous and in need of improvement.[4] These histories may be obtained by a number of different practitioners with varying skills and recorded on different forms and in different places in the medical record. In some cases the only history recorded is the medicines ordered on the inpatient medication chart.

Prescribing medicines on admission, transfer and discharge

Errors can be introduced into a patient's medication regimen whenever there is a transfer of care, particularly on:

- admission to hospital
- transfer from the emergency department to other wards, or the intensive care unit
- transfer from intensive care unit or operating theatre to the ward
- transfer from hospital to home or another facility, such as a residential aged-care facility.

Discrepancies commonly occur between the drugs a patient is taking on admission and those ordered on the medication chart. Literature reviews report unintentional discrepancies of 30–70% between the medicines patients were taking before admission and their prescriptions on admission.[5] In a recent study, 26.6% of these discrepancies were attributable to inadequate or incorrect information in primary care medicines lists including general practitioner referrals and printouts of medicines.[11]

Patients over the age of 65 years and those taking several prescription medicines have a significantly increased risk of medication errors.[12] Internal hospital transfer of care also carries considerable risks. At least one in six patients have one or more clinically significant medication discrepancies on transfer, for example when a patient is transferred from intensive care to a general ward.[13-15] Patients at high risk for these discrepancies include those for whom a comprehensive medication history has not been taken by the time of transfer, those with a greater number of medicines taken before admission, and those prescribed multiple medicines at the time of transfer.[14] Omission of a medicine with a valid indication is the most common unintentional discrepancy[14] and around half of these errors may not be detected before they affect the patient.[15]

Discrepancies also commonly occur at discharge when prescriptions are written and discharge summaries prepared. One Australian study has reported 15% of drugs intended to be continued were omitted on the discharge prescription.[16] Another found 12% of patients had one or more errors in their discharge prescription, including unintentional omissions and continuation of drugs which had been ceased.[17] Patients with one or more drugs omitted from their discharge summary have 2.31 times the usual risk of re-admission to hospital.[18]

Consequences of medication errors

Case 1

A 67-year-old woman with a regular general practitioner was prescribed several medications, including atenolol 50 mg daily, after a myocardial infarction. Six months later she saw a cardiologist for a review of her treatment. She was asymptomatic, but the cardiologist prescribed metoprolol 50 mg twice daily. The cardiologist did not have a complete list of her medicines. As she was now taking two beta blockers, the patient subsequently developed symptomatic bradycardia.

Case 2

An elderly man was admitted to hospital via the emergency department. The patient had recently started warfarin for atrial fibrillation so his INR was measured. The INR was 4.0 and the decision to 'withhold warfarin until INR is therapeutic' was documented in the patient's notes. No warfarin was ordered during the admission. The discharge prescription and summary were written from the inpatient medication chart so did not include warfarin. There was no reconciliation with the admission history. A medicines list for the patient was prepared by hospital pharmacy staff from the discharge prescription and placed in the bag with a month's supply of discharge medicines. No follow-up appointment was made with the general practitioner. Five days later the patient suffered a stroke.

What is medication reconciliation?

Medication reconciliation is a process designed to improve communication and promote teamwork. This has the objectives of preventing medication errors associated with the handover of care[19] and maintaining continuity of care. It is described as the formal process of obtaining, verifying and documenting an accurate list of a patient's current medicines on admission and comparing this list to the admission, transfer and discharge orders, to identify and resolve discrepancies.[13,20,21] At the end of each episode of care the verified information is transferred to the next care provider and provided to the patient or carer.[21] This information includes changes made to the medicines during the episode of care. There are a number of discrete steps (Fig. 1). The process is based on the safety principle of independent redundancies – having independent checks, generally by different providers, for key steps in the process.[13] The process aligns with the principles recommended to achieve continuity of medication management in Australia.[22]

Fig. 1 **Steps in the medication reconciliation process on hospital admission**

Step 1. Obtain a best possible medication history

Compile a comprehensive list of medicines the patient is currently taking from interview with patient, referral letters and other sources. Include:

- prescription, over-the-counter and complementary medicines
- medicines name, dose, route, and frequency
- duration of therapy
- indication for use.

→

Step 2. Confirm the accuracy of the history

Verify the medication history:

- review patient's medicines list
- inspect patient's medicines containers (including blister packs)
- contact other prescribers and pharmacist
- communicate with carer or family
- review previous health records (e.g. discharge summaries).

→

Step 3. Reconcile history with prescribed medicines

Compare the history with the medicines ordered, taking into consideration the patient's medical conditions

Resolve discrepancies with prescriber and document any changes

→

Step 4. Supply accurate medicines information

When care is transferred to receiving clinician, patient or carer, provide a list of current medicines and reasons for any changes

The best possible medication history

A 'best possible medication history' is the cornerstone of the medication reconciliation process. It is described as a comprehensive drug history obtained by a clinician that includes a thorough history of all regular medicines used, including non-prescription and complementary medicines, and is verified by more than one source. A structured process for taking the history, that involves the patient or carer or family, using a checklist to guide the interview, and that verifies the history with information from a number of different sources, provides the best assessment of the drugs a patient takes at home.[4]

Sources used to obtain a comprehensive history are listed in Fig. 1 (step 2). Patients being admitted to hospital should be advised to take their medicines containers and current medicines list.

Ideally the best possible medication history is completed before any drugs are ordered and is used when the medication chart is written up. For unplanned admissions the history is usually completed after the initial medication orders have been written and is used to reconcile the orders.

In the community the general practitioner can refer to the community pharmacy for a list of dispensed medicines or request a Home Medicines Review to determine the medicines currently taken. This best possible medication history should be reconciled with the current medication list in the patient's record and their condition.

Standardised reconciling form

A standardised form for recording the best possible medication history and reconciling any discrepancies is essential for effective medication reconciliation. Whether electronic or paper based, the form should be kept in a consistent, highly visible position in the patient's notes and be easily accessible by all clinicians when writing medication orders and reviewing the patient.[19]

In Australia the National Medication Management Plan* can be used to record the history and reconcile medication orders in patients admitted to hospital.

Electronic solutions

Computerised systems (e-prescribing) may prevent many of the medication errors that occur at transfers of care but these systems are not without their problems. They still require someone to enter an accurate list of drugs and allergies. Medication lists in electronic records can lag behind prescription changes and be incomplete.[12] For example, they may only contain the medicines prescribed in a particular system, and not include non-prescription products or medicines prescribed by other practitioners. Outdated, unverified or inaccurate information may be transferred indefinitely when using copy-and-paste facilities, so reconciliation is still required.[13]

Reconciling medicines

Medicines should be reconciled as soon as possible,[5] at least within 24 hours of a patient's admission to hospital or earlier for high risk drugs.[19] This involves a clinician comparing the history against the medication orders at admission, transfer or discharge to identify any variances and bring them to the attention of the

* www.safetyandquality.gov.au/internet/safety/publishing.nsf/Content/PriorityProgram-06_MedRecon

prescriber, taking into consideration the patient's clinical condition. Any changes to orders are documented. Whoever performs the task should be trained and competent in the process.

In the community, medication reconciliation should occur on receipt of information about the discharge medication. The general practitioner can compare the medication history in the patient's notes with the discharge medicines list provided by the hospital, reconciling any differences and updating the patient's record. Similarly when changes are made to a patient's medicines such as dosage alterations, medicines ceased or new medicines prescribed, the current medication list in the patient's record should be reviewed and updated. This reduces the risk of inaccurate medication information being transferred to other care providers in referrals. Providing patients or carers with an updated list when medicines are changed and encouraging them to maintain their own medicines list is an important component of the medication reconciliation process. A medicines list is available from NPS.*

Involving patients in medication reconciliation

Engaging the patient is one of the best strategies to prevent reconciliation errors and a patient-centred approach to medication reconciliation is recommended. When patients present a list of their medicines, or the medicines themselves, on admission to hospital the risk of medication errors and harm is reduced.[12] Any discrepancies should be discussed with the patient, and enquiries made about medicines prescribed by other prescribers and any over-the-counter or complementary medicines they are taking.

Evidence for effectiveness of medication reconciliation

Individual hospital studies and a number of large-scale initiatives in the USA and Canada have shown that medication reconciliation significantly reduces medication errors and adverse events. Errors prevented by medication reconciliation include inadvertent omission of therapy, prescribing a previously ceased medicine, the wrong drug, dose or frequency, failure to recommence withheld medicines and duplication of therapy after discharge. Implementing formalised medication reconciliation at admission, transfer and discharge reduces medication errors by 50–94%[3,13,15,20] and reduces those with the potential to cause harm by over 50%.[3,23] The process is also associated with improved patient outcomes and a tendency for reduced readmissions.[18]

Efficiency

A standardised process for medication reconciliation reduces the work associated with the management of medication orders. Time savings for nurses of 20 minutes per patient at admission and pharmacists of 40 minutes per patient at discharge have been reported.[20]

Recognising the importance of medication reconciliation

A formalised system of medication reconciliation could have prevented the events described in the cases. In case 2 if the doctor's plan to recommence the warfarin had been documented in the patient's medication management plan, the error would have been identified if the plan had been used to reconcile the drugs ordered on discharge.

Conclusion

The process of medication reconciliation, using a formalised structured approach involving patients and carers and conducted in an environment of shared accountability, can reduce the morbidity and mortality of medication errors that occur at interfaces of care. Medication reconciliation is a cost-effective use of the health dollar and an important element of patient safety. ◁

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Q:

SELF-TEST QUESTIONS

True or false?

1. Patients who have one or more medicines omitted from their discharge prescription are twice as likely to be readmitted to hospital.
2. At least 27% of prescribing errors result from a failure to take a complete medication history.

Answers on page 35

* www.nps.org.au/consumers/tools_and_tips/medicines_list (also available as a mobile phone application)

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National Medicines Symposium 2012

NPS announces the seventh National Medicines Symposium, to be held on 24–25 May 2012 at the Sydney Convention and Exhibition Centre. The symposium provides the opportunity to network and share your expertise at the leading symposium on quality use of medicines in Australia. It brings together the partners to Australia's National Medicines Policy along with international representatives to learn, discuss and debate contemporary quality use of medicines issues. The theme is 'Building a medicinewise community'.

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ARTICLE

Safe prescribing of opioids for persistent non-cancer pain

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Key words
adverse effects, opiates, substance use disorder

Aust Prescr 2012;35:20–4

SUMMARY

A judicious approach in considering opioid therapy and choosing an appropriate opioid is needed.

After an initial opioid trial, therapy should only be continued when there is reasonable evidence that it is effective and safe.

The evidence for harm associated with long-term opioid prescribing is mounting while there is little evidence to support long-term efficacy. In many cases, reducing and eventually stopping opioid therapy may be the best course of action.

Commitment by both the prescriber and the patient to a treatment plan which includes regular reviews is essential if opioid therapy is prolonged.

Introduction

The prevalence of opioid prescribing in Australia, particularly for persistent non-malignant pain, has been steadily increasing.[1] There is emerging evidence of a corresponding increase in deaths where opioids were detected.[2] Similar trends have been reported in the USA with an alarming escalation in opioid-related deaths.[3] Safe opioid prescribing is best defined by the principles for the quality use of medicines in Australia's National Medicines Policy.[4] This recommends that any reason to prescribe needs to be considered judiciously,[5] then appraised for appropriateness, and thereafter monitored for safety and efficacy.

State legislation

To prescribe opioids beyond eight weeks, most states and territories require the prescriber to have a state permit. However in NSW, a permit is only needed for prescribing opioids to patients with drug dependence. All other jurisdictions need to be notified for any patient who is drug dependent.

Considering opioid treatment

There is little evidence for the efficacy of long-term opioid use in persistent non-malignant pain and in trials (up to three months) many patients experienced adverse drug effects.[6] However, there is expert consensus that opioid analgesics be considered when other treatments have been inadequate.

Before undertaking a longer-term period of opioid treatment, the patient should be assessed following an initial trial period, for example a month (see Box). After that, the prescriber should identify evidence of improved patient function correlated with opioid use. It is imperative that the patient give informed consent at the start of the trial, acknowledging the possibility of a negative outcome and withdrawal of therapy.

The definition of pain[7] as 'an unpleasant sensory and emotional state' reminds us that a significant proportion of a patient's suffering will be related to the emotional contribution to their pain perception. Some patients may report that all treatments have failed including physical and psychological therapy, however this may represent the patient's resistance to engage in appropriate treatment and not necessarily a 'failure of all therapies'. Indeed, physical and psychological interventions may vary in their effect and appropriateness for individual patients, just as drug therapies do.

Chronic pain and depression often coexist and depression may be a reason why some patients respond poorly to initial treatments. If a patient is not responding to opioids, other pain management strategies may need to be considered including referral for an assessment at a specialist pain clinic.

Previous or current substance use disorder increases the risk for addiction and related problems. Screening tools may help to identify this.[8] Inadequate compliance with previous therapy, extreme frustration with pain symptoms, inappropriate pursuit of a 'cure', requests based on the second-hand experience of other patients and the patient who predominantly conceptualises pain management as taking medication (chemical coping) would all be reasons for increased caution. The Royal Australasian College of Physicians Prescription Opioid Policy (2009) is freely available to download from www.racp.edu.au.[9] It provides an excellent review and guidelines for managing chronic non-malignant pain.

Relative contraindications

There are numerous contraindications to opioid use. The risk of developing opioid dependence during long-term opioid analgesic prescribing in some patients is significantly increased, for example in

those with a history of substance use disorder. To avoid iatrogenic dependence, consult with a pain or addiction medicine specialist when a patient develops 'tolerance' and is seeking a dose increase, particularly when any problematic opioid-related behaviours appear.

Other factors that need to be considered when assessing the patient include the following:

- previous poorly tolerated opioid treatment
- drugs with potential interactions, e.g. tramadol with other serotonergic drugs such as selective serotonin reuptake inhibitors can cause serotonin toxicity
- psychiatric risk – previous intentional overdoses
- depression
- dementia
- obstructive sleep apnoea
- severe gastro-oesophageal reflux disease or gastrointestinal hypomotility
- organ failure, e.g. renal impairment may result in morphine accumulation
- other existing conditions, e.g. many patients with porphyria have sensitivity to several opioids
- occupations, e.g. patients working in the aviation or mining industry and other situations that impose **zero tolerance** for any drugs of dependence.

Choosing an appropriate opioid

An appropriate opioid best avoids the risk of drug interactions, disease interactions and patient 'interactions' (for example patients may favour 'tamper-resistant' options if children are at home).

Oral long-acting opioids are recommended because short-acting opioids wear off quickly (particularly given tolerance over time), require frequent repeat dosing and, if used chronically, may cause 'analgesic rebound' or break-through pain. Long-acting transdermal and sublingual opioid formulations might be considered for patients who have problems with swallowing tablets.

Patients with drug dependence strongly prefer short-acting drugs with faster onset of action and with higher peak blood levels (that is, quick reward). They will often state a preference for immediate-release preparations or resist taking long-acting drugs.

The chronic use of injectable drugs is inappropriate for persistent pain because recurrent injections lead to tissue injury (which reduces drug absorption), carry the risk of infection as a consequence of chronic injecting and have a greater risk for addiction and diversion*. People who are drug dependent typically manifest a very strong preference for their drug of choice and such patients can be remarkably convincing in their efforts to persuade a compassionate doctor that such therapy is the only effective treatment. Pethidine is now generally viewed as a poor opioid analgesic in comparison with most others now available and is inappropriate for persistent pain.[10]

Patient reports of 'drug allergy' might instead be dose-related adverse effects like nausea or pruritis and therefore dose reduction is suggested rather than avoidance, or referral to clinical immunology for specific drug sensitivity testing. Sometimes the latter may be necessary if options are restricted by the patient reporting 'allergy' to multiple opioids particularly if there is strong patient preference for treatment with a specific drug, for example pethidine.

Evaluating the efficacy of ongoing opioid therapy

After a successful initial therapeutic trial, continuing opioid treatment requires commitment to a treatment plan of regular reviews of efficacy and safety. A common problem faced by some doctors who

Box **Trialling opioids in patients with non-malignant pain**

Assess the potential merits and contraindications for opioids in patients unresponsive to other 'first-line' treatments
Consider whether depression is a complication and needs treatment before proceeding with a trial of opioids
Formulate a treatment plan for the next month which the patient agrees to. Include weekly reviews and explain the possibility that treatment may not prove helpful and may need to be discontinued. Have the patient fill in a Brief Pain Inventory.
Start treatment with a long-acting opioid of moderate efficacy
Recommend the patient keep a daily diary to monitor activities and pain-related impairment
Ensure the opioids will be safely stored in the home and secure from children
Establish a dialogue with the pharmacist
Review the patient weekly with a family member and the patient's diary. Appraise treatment efficacy with a Brief Pain Inventory and witness accounts (family members, pharmacist). If the patient has a poor response, consider a dose change. If they are unable to tolerate treatment, consider switching to an alternative opioid starting at a low dose.
Monitor for adverse effects (e.g. developing constipation, sleep problems, drowsiness, miosis, slurred speech)
Recommend the patient avoids driving until further assessment of their opioid therapy. Consider baseline Epworth Sleepiness Scale (ESS) to assess possible daytime somnolence. Ask the spouse about any current snoring or sleep problems (opioids may increase these conditions when taken at night).

* Diversion of a drug means that it has been given or sold to, or taken by, a person for whom it was not prescribed

have been formally investigated for their opioid prescribing has been an apparent deficient or absent opioid treatment plan. Just as treating hypertension requires periodic measurements of blood pressure, continuing opioid therapy requires documentation of ongoing monitoring of patient function. A pain management form[11] for patients can be used as a written management plan. Sustained improvement that can be correlated with opioid therapy, without unacceptable adverse effects, constitutes reasonable justification to continue therapy. Correlating opioid therapy with functional improvement is more important than reduction of patient-perceived pain. Relying on a patient's own opinion of their improvement is subjective. Better evidence includes examination of the patient's functioning during regular clinic attendance, reports from their pharmacist and family together with the patient's self-report and use of validated questionnaires such as the Brief Pain Inventory.[12]

Correlating opioid therapy with functional improvement is more important than reduction of patient-perceived pain

If prescribing beyond 12 months, a second opinion from a specialist (for example in pain medicine) is required to fulfil Pharmaceutical Benefits Scheme Authority indications.

Adherence

It is also important to assess the patient's adherence to treatment by reports from reliable informants. Occasional urine drug screening may be useful. If a patient reports benefit from an opioid and yet one or more urine drug screens show it is not present, diversion should be suspected. There is evidence that even some cancer patients taking opioids have diverted these drugs.[13] The practice of medication swapping, borrowing and sharing also needs to be considered as these are not uncommon behaviours.[14] Collaboration with the patient's community pharmacist is also a helpful way of improving adherence.

Monitoring the safety of opioids

Opioids are not just analgesics, they have a range of effects including endocrine, immunological, cognitive and emotive. Long-term opioid use is associated with numerous adverse reactions (listed in Table 1).[15] The continuing management plan needs to incorporate a process of regular review for the risk and occurrence of adverse drug events. This includes monitoring the patient physically, mentally and in regard to areas of important functioning, for example the ability to drive, work, participate in hobbies, and for possible aberrant drug-related behaviours.[8]

Opioid dosages over 120 mg (mg morphine equivalent) correlate with an increased risk of mortality.[16] The comparative safety of opioids compared to other drugs (for example non-steroidal anti-inflammatory drugs) in older adults is questionable[17] and prescribing high-dose opioids long term carries greater risk for misuse.[18] While chronic pain of itself does not kill, prescribing opioids particularly in high doses and in conjunction with other sedatives like benzodiazepines does increase the mortality risk.[2,3,16,18]

Table 1 presents strategies for managing potential opioid-related adverse effects. Perceived risks (noting an absence of adverse opioid effects) and how they are addressed and managed should be documented in the treatment plan during regular clinical reviews.

Stopping opioids

When longer-term opioid treatment goals have not been met, treatment should be discontinued. This process is facilitated by having a pre-arranged treatment plan with the patient. Explain the need to stop opioids and set a reasonable timeline for gradual reduction of the dose (for example 10–20 mg morphine equivalent per week). Review the patient weekly and ensure they receive additional support during this time (for example supportive therapies like massage, hydrotherapy and counselling) and monitor the patient's mental state, as some people can experience mood disturbance during opioid withdrawal. In some cases, advice from a pain and/or addiction medicine specialist may be warranted. Temporary 'setbacks' may occur but should be contained and the goal of completing opioid withdrawal should be maintained.

Conclusion

Opioids are not universal painkillers but may have a role in managing persistent non-malignant pain for appropriately selected patients. Once commenced, ongoing evaluation of safety (adverse opioid events) and efficacy (with documentation) should guide clinical management. A treatment plan that incorporates the possibility of, and process for, stopping opioids is essential. For many patients, long-term opioid use may not prove safe and effective. ◁

Dr McDonough occasionally acts as a medical adviser to Reckitt-Benckiser regarding the use of buprenorphine in opioid addiction treatment.

Q:

SELF-TEST QUESTIONS

True or false?

3. Tramadol should be avoided in patients taking selective serotonin reuptake inhibitors.

4. Opioid doses above 200 mg are associated with an increased risk of death.

Answers on page 35

Table 1 **Managing opioid-induced adverse effects** [15]

ADVERSE EFFECT	SUGGESTED STRATEGY
Gastrointestinal	
Nausea and vomiting	Reduce dose, consider alternate formulation (sublingual, transdermal), exclude chronic constipation
Chronic constipation and related sequelae including abdominal pain, reflux, haemorrhoids, colonic hypomotility	Recommend regular bulking agent, extra fluids, non-osmotic laxatives
Reduced salivary flow posing dental problems	Six-monthly dentist reviews, brushing and flossing teeth, extra fluoride treatment, encourage salivary flow after meals, diet
Gastro-oesophageal reflux disease	Specific treatment e.g. proton pump inhibitor such as omeprazole
	Consider reducing or stopping opioids
Neurological	
Impaired cognition	Periodic assessment, mini-mental state examination
Impaired coordination	Heel-toe gait testing
Sedation	Consider monitoring with Epworth Sleepiness Scale (for excessive daytime somnolence) and with family and other witness accounts (e.g. pharmacist)
	Consider possibility of drug interaction (e.g. benzodiazepines) and review dosages and need
Hyperalgesia	Periodic assessment, avoid doses >120 mg (mg morphine equivalent)
Endocrine	
Hyperprolactinaemia (and galactorrhea)	Monitor prolactin
Hypogonadism	Monitor testosterone
Osteoporosis	Monitor from baseline, check vitamin D status, seek specialist guidance
Respiratory	
Exacerbation of obstructive sleep apnoea	Consult respiratory physician
Inducing central sleep apnoea	Likely contraindication (e.g. methadone), reduce dose, sleep study (polysomnography), consult respiratory physician
Respiratory depression	Especially in patients with type 2 respiratory failure (CO_2 retention) and those on home oxygen therapy
	Deterioration requires specialist intervention and probable opioid discontinuation
Cardiovascular	
Prolonged QTc	Electrocardiogram (particularly with methadone and oxycodone)
Psychiatric	
Mood disorder	Monitor from baseline, reduce dose and review
Addiction	Consult addiction specialist, consider referral to methadone program
Overdosage	Prescribe small amounts (e.g. weekly supply), ensure only one prescriber and likewise pharmacist, assess patient for depression
Other	
Fluid retention and oedema	Document, reduce dose, restrict sodium, consider a diuretic
Occupational and driving impairment	Establish baseline and review with reference to reliable co-informants
Diversion potential	Consider 'tamper-resistant' preparations, require patient to have secure storage (e.g. locked metal box), designate one pharmacy, note on script, fax script in advance
	Prescribers can also check with the Prescription Shopping Information Service (www.medicareaustralia.gov.au/provider/pbs/prescription-shopping/index.jsp#N10058)

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Book review

Introduction to pharmaceutical calculations. 3rd ed.

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Rees JA, Smith I, Smith B.

London: Pharmaceutical Press; 2011. 245 pages.

Price: $76, members of the Pharmaceutical Society of Australia $59

The third edition of this British book, written by pharmacy educators, is an introduction to drug dosage and other pharmaceutical calculations. Each chapter contains learning objectives, numerous worked examples, sample questions and answers. It also includes new chapters on accuracy of measurement and updated worked examples.

However, I have reservations about its usefulness for Australian pharmacy students. I can envisage Australian pharmacy students, who come with high levels of mathematics skills, becoming quite annoyed at the rather simplistic content.

Most pharmacy schools have pharmaceutical calculations taught and assessed over the four years of the course and there are further assessments by the Pharmacy Board of Australia as part of pharmacists' registration examinations during their internship year.

This book also suffers from significant omissions, such as pharmacokinetic and clinical calculations that are relevant to modern-day pharmacy practice. Many of the examples are antiquated and the use of chloroform water (which appears in many examples) is banned in Australia. Again, in the Australian context, devoting a chapter on converting degrees Fahrenheit to Celsius and vice versa is probably irrelevant.

I cannot recommend this book as a text for pharmacy students in Australia.

Emergency drug doses – PBS* doctor's bag items

DRUG	INDICATION	DOSE
Adrenaline (1000 microgram in 1 mL injection equivalent to 1:1000) 1000 microgram = 1 mg	Anaphylaxis[1]	5–10 microgram/kg IM approximates to: Adults: <50 kg 0.25–0.5 mL >50 kg 0.5 mL Children: 10 kg (1–2 years) 0.1 mL 15 kg (2–3 years) 0.15 mL 20 kg (4–6 years) 0.2 mL 30 kg (7–10 years) 0.3 mL Repeat dose every 5 minutes if no response
	Cardiac arrest	Adults: 0.5–1 mg IV Flush with normal saline to aid entry into the circulation Children: 10 microgram/kg slow IV (Dilute 1 mL adrenaline injection 1:1000 with 9 mL sodium chloride (0.9%) and give 0.1 mL/kg)
Atropine (0.6 mg in 1 mL injection)	Severe bradycardia, asystole	Adults: 1 mg IV, repeat every 3–5 minutes until desired heart rate is reached or to a maximum of 3 mg Children: 20 microgram/kg IV (maximum dose 0.5 mg), repeat every 5 minutes until desired heart rate is reached or to a total maximum of 1 mg
Benztropine (2 mg in 2 mL injection)	Acute dystonic reactions	Adults: 1–2 mg IM or IV Children >3 years: 20 microgram/kg IM or IV (maximum 1 mg). Repeat after 15 minutes if needed.
Benzylpenicillin (600 mg or 3 g powder, dissolve in water for injections)	Severe infections, including suspected meningococcal disease	Adults and children ≥10 years: 1.2 g IV or IM Children aged 1–9 years: 600 mg IV or IM Children <1 year: 300 mg IV or IM
Chlorpromazine (50 mg in 2 mL injection)	Acute psychosis, severe behavioural disturbance	Avoid parenteral use – injections cause pain and skin irritation. Use haloperidol instead. Adults: If there is no alternative, chlorpromazine 25–50 mg (12.5–25 mg in the elderly) can be given by deep IM injection (buttock or deltoid)
Dexamethasone sodium phosphate (4 mg in 1 mL injection)	Acute severe asthma[2]	Adults: 4–12 mg IV slowly
	Severe croup	Children: 0.15 mg/kg IM if oral route is not possible
	Bacterial meningitis	Start before or at the same time as antibiotic Adults: 10 mg IV Children aged >3 months: 0.15 mg/kg IV
Diazepam (10 mg in 2 mL injection)	Severely disturbed patients	Adults: 5–10 mg IV over 1–2 minutes (halve dose in elderly) in a large vein. Repeat if necessary every 5–10 minutes (maximum 30 mg).
	Seizures	Adults: 10 mg IV slowly in a large vein. Repeat once if necessary. 10–20 mg rectally if IV access not possible. Repeat once if necessary. Children: 0.2–0.3 mg/kg IV slowly in a large vein (maximum 10 mg). Repeat once if necessary. 0.3–0.5 mg/kg rectally (maximum 10 mg). Repeat once if necessary.
Dihydroergotamine (1 mg in 1 mL injection)	Severe migraine	Adults: 0.5–1 mg SC or IM. Repeat every hour if needed (maximum 3 mg daily).

* Pharmaceutical Benefits Scheme

FEATURE Emergency drug doses – PBS doctor's bag items

DRUG	INDICATION	DOSE
Diphtheria and tetanus booster vaccine (0.5 mL pre-filled syringe)	Tetanus prophylaxis	Adults and children >8 years: 0.5 mL IM
Frusemide (20 mg in 2 mL injection)	Left ventricular failure, acute pulmonary oedema	Adults: 20–40 mg IV slowly or IM
Glucagon (injection kit containing 1 mg glucagon and 1 mL solvent in syringe)	Severe hypoglycaemia	Adults and children >5 years: 1 mg SC, IM or IV Children <5 years: 0.5 mg SC, IM or IV
Glyceryl trinitrate (400 microgram per dose, 200 doses as sublingual spray)	Acute angina, acute left ventricular failure	Adults: 1–2 sprays under the tongue. Repeat after 5 minutes if needed (maximum 3 sprays).
Haloperidol (5 mg in 1 mL injection)	Acute psychosis, severe behavioural disturbance	Adults: 2–10 mg IM (0.5–2 mg in the elderly)
Hydrocortisone sodium succinate (100 mg or 250 mg with 2 mL solvent for injection)	Acute severe asthma	Adults: 100 mg IV Children: 4 mg/kg IV
	Anaphylaxis	Adults: 100 mg IV or IM Children: 2–4 mg/kg IV
	Acute adrenal insufficiency	Adults: 100 mg IV or IM Children 1–12 years: 50 mg IV or IM Children 1–12 months: 25 mg IV or IM
Lignocaine (100 mg in 5 mL injection)	Sustained ventricular tachycardia	Lignocaine has serious adverse effects including the potential to worsen arrhythmia and cardiac failure. Do not use outside of hospital. Adults and children: 1 mg/kg IV over 1–2 minutes. Repeat after 5 minutes if needed.
Metoclopramide (10 mg in 2 mL injection)	Nausea and vomiting	Adults: IV or IM >60 kg 10 mg starting dose 30–59 kg 5 mg starting dose (maximum 0.5 mg/kg daily) Not generally recommended in children as there is a risk of extrapyramidal adverse effects
Methoxyflurane (3 mL plus inhaler)	Pain after acute trauma	Adults and children (who are able to use the device, usually ≥ 5 years): 6–8 breaths at a time (maximum 6 mL/day)
Morphine sulfate (15 mg or 30 mg in 1 mL injection)	Severe pain	Adults: SC or IM starting at lower dose <39 years 7.5–12.5 mg 40–59 years 5–10 mg 60–69 years 2.5–7.5 mg 70–85 years 2.5–5 mg >85 years 2–3 mg Can also be given as IV increments of 0.5–2 mg titrated to effect Children >1 year and <50 kg: 0.05–0.1 mg/kg SC or IM
Naloxone (2 mg in 5 mL injection)	Opioid overdose	Adults and children: 0.4–0.8 mg IV, IM or SC repeated as necessary Neonates born with low APGAR scores to mothers taking opioids: 0.1 mg/kg IV, IM or SC. Repeat if needed.
Procaine penicillin (1.5 mg in 3.4 mL injection) This should read (1.5 g in 3.4 mL injection) Corrected May 2013	Severe infections (only suitable for infections where prolonged low concentrations are appropriate)	Adults: 1–1.5 g by deep IM injection Children: 50 mg/kg by deep IM injection

DRUG	INDICATION	DOSE
Prochlorperazine (12.5 mg in 1 mL injection)	Nausea and vomiting, vertigo	Adults: 12.5 mg IM or IV
Promethazine hydrochloride (50 mg in 2 mL injection)	Allergic reactions	Adults and children >12 years: 25–50 mg IM Children >2 years: 0.125 mg/kg IM
	Nausea and vomiting	Adults and children >12 years: 12.5–25 mg IM
Salbutamol inhaler (100 microgram per dose, 200 doses)	Acute asthma, bronchospasm	Adults and children: 4 puffs (400 microgram) via spacer. Repeat after 4 minutes if needed. If still no improvement, continue giving 4 puffs every 4 minutes until ambulance arrives.
Salbutamol nebuliser solution (2.5 mg or 5 mg in 2.5 mL per dose, 30 doses)	Acute asthma, bronchospasm	Adults and children >2 years: 2.5–5 mg by nebuliser as required Children <2 years: 0.1 mg/kg up to 2.5 mg by nebuliser as required For anaphylaxis give 5 mg by nebuliser to adults and children, repeat if required
Terbutaline (500 microgram in 1 mL injection)	Acute asthma	Adults: 250 microgram SC Children: 5 microgram/kg SC
Tramadol (100 mg in 2 mL injection)	Pain	Adults: 50–100 mg IV over 2–3 minutes or IM
Verapamil (5 mg in 2 mL injection)	Paroxysmal supraventricular tachycardia in patients who are **not**: - taking beta blockers - having an infarction - in second or third degree atrioventricular block	Do not use outside of hospital Adults: 5 mg IV slowly (over at least 3 minutes), repeat after 5–10 minutes if no response Children: 0.1–0.3 mg/kg IV, repeat after 30 minutes if no response (maximum 5 mg)

* Pharmaceutical Benefits Scheme

IM intramuscular IV intravenous SC subcutaneous

A guide to paediatric weights 10 kg at 1–2 years 15 kg at 2–3 years 20 kg at 4–6 years 30 kg at 7–10 years

PBS* doctor's bag items for palliative care patients

These drugs should only be used after consultation with a palliative care specialist

DRUG	INDICATION	DOSE
Clonazepam (oral liquid containing 25 mg in 10 mL)	Preventing seizures, hiccups	Adults: 0.25–1 mg orally or sublingually
Hyoscine butylbromide (20 mg in 1 mL injection)	Noisy breathing and secretions	Adults: 10–20 mg subcutaneously

* Pharmaceutical Benefits Scheme

Acknowledgement: Australian Prescriber thanks the staff at the Australian Medicines Handbook for their help in preparing this chart.

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Volume 3, Number 1, February 2012

In this issue

Pneumovax 23 – updated revaccination recommendations

In April 2011 the Therapeutic Goods Administration (TGA) advised health professionals not to administer a second or subsequent dose of Pneumovax 23 vaccine pending the outcome of a review of an apparent increased rate of injection site reactions following administration of the second dose. This review has now been completed and the TGA is advising health professionals not to routinely revaccinate immunocompetent individuals. Revaccination of patients at high risk of serious pneumococcal disease should be in accordance with the Product Information (PI).

Pneumovax 23 is used to prevent life-threatening infections by pneumococcal bacteria. The TGA review noted that the adverse events observed were consistent with the known high rates of local reactions which occur more commonly after a repeat dose of Pneumovax 23. The review concluded that the adverse events were not due to a problem with the vaccine manufacturing or handling. The outcomes from the review are available on the TGA website.[1]

Updated TGA advice about revaccination

The TGA is advising that revaccination with Pneumovax 23 should be undertaken in accordance with the approved PI.

Revaccination:

- should not be given routinely to immunocompetent individuals; and
- should be considered for patients at a high risk of serious pneumococcal disease, provided that at least five years have passed since the previous dose of Pneumovax 23.

This advice differs from that in the current Australian Immunisation Handbook,[2] which recommends routine revaccination five years after the first dose. The Australian Technical Advisory Group on Immunisation has reviewed the place of Pneumovax 23 in the National Immunisation Program and their updated recommendations have been published at www.immunise.health.gov.au.

Adverse reactions to Pneumovax 23

Pneumovax 23 is known to be associated with a high rate of local injection site reactions, which can result in extensive swelling and pain that can limit the use of the patient's arm. Cellulitis-like reactions and abscesses can also occur, however these are rare.

Further information about possible adverse reactions is available in the Pneumovax 23 PI.[3]

Advice is specific to Pneumovax 23

This advice does not apply to Prevenar, Prevenar 13 and Synflorix pneumococcal conjugate vaccines.

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2. NHMRC. The Australian Immunisation Handbook. 9th ed. Canberra: Australian Government; 2008.
3. Pneumovax 23 Product Information. Merck Sharp & Dohme (Australia) Pty Limited. 2011 Aug.

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

TGA Health Safety Regulation

Caveat emptor 'buyer beware' – the risks of purchasing unregistered medicines online

The inherent dangers of purchasing unregistered products via the internet have been highlighted recently with a series of serious adverse events, including disfigurement and death, reported to the TGA.

Since 1 July 2011 the TGA has published nine safety alerts related to herbal products bought over the internet and which laboratory tests have found to contain prescription medicines. The most common herbal products reported are for slimming or weight loss and erectile dysfunction.

Herbal slimming products

Tests of herbal slimming and weight loss products purchased over the internet by the TGA Laboratories have shown varying amounts of the anorectics sibutramine and fenfluramine, and the laxative phenolphthalein. All of these products have been withdrawn from the Australian market for safety reasons, including increased risk of cardiac events and stroke (sibutramine in 2010), reports of valvular heart disease and pulmonary hypertension (fenfluramine in 1997) and concerns regarding carcinogenicity (phenolphthalein).

In addition, TGA laboratory testing has identified propranolol, nifedipine and ephedrine in some of these products.

Herbal erectile products

There have also been several safety alerts since 1 July 2011 related to herbal products for improving sexual function, which on testing have been found to contain sildenafil (also known as Viagra). The TGA has also identified or received reports of additional prescription medicines, such as glibenclamide, being included in these herbal products bought overseas and advertised on the internet. When taken at high doses, glibenclamide-containing products have resulted in severe hypoglycaemia and death.

Injectable cosmetic agents

Injectable cosmetic products such as dermal fillers and botulinum toxin-like products are being increasingly marketed on the internet as 'do it yourself' cosmetic kits.

The TGA is aware of consumers who have purchased these 'do it yourself' cosmetic kits and experienced severe reactions, such as anaphylactic reactions and facial scarring. Some consumers experiencing these adverse events have required ongoing medical care. Use of these agents can lead to facial swelling, infection, scarring and severe abscess formation that can, in some instances, require surgical intervention. Reports of these reactions have also appeared in the mainstream media.[1]

Information for health professionals

Herbal products available on international websites are not regulated by the TGA and therefore may not meet the same standards of safety and quality as products that are listed on the Australian Register of Therapeutic Goods, and approved by the TGA for sale in Australia.

The TGA advises consumers that they should exercise extreme caution about purchasing medicines from overseas internet sites, as products purchased in this way may contain undisclosed and potentially harmful ingredients.

Health professionals are in a unique position to discuss the use of health products with their patients and are encouraged to discuss the potential problems associated with the use of medicines and medical devices purchased over the internet.

Health professionals are also encouraged to ask their patients about any products they may be using to manage or prevent a condition, and the source of the product, when managing health related problems.

More information about purchasing via the internet, personal importation of medical goods and counterfeit products can be found at www.tga.gov.au/consumers/information-online-overseas.htm.

Information about the products discussed in this article can be found at www.tga.gov.au/safety/alerts-current.htm, which is updated regularly with new TGA safety information, including product recalls and alerts. Subscribe to these free alerts by visiting www.tga.gov.au/newsroom/subscribe-tga-safety info.htm.

Health professionals are encouraged to report any problems associated with a medicine or medical device to the TGA via the 'Report a Problem' link on the TGA website.

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MEDICINES SAFETY UPDATE

Citalopram and QT prolongation – important changes to the dosing recommendations

A study of citalopram's effect on cardiac conduction, which showed dose-dependent QT prolongation with the medicine, has led to the recommended maximum daily dose of citalopram being reduced to 40 mg, along with other important changes to dosing recommendations for citalopram.

Citalopram is a selective serotonin reuptake inhibitor indicated for the treatment of major depression. There are a number of citalopram-containing products with different trade names registered in Australia.

A recent study has found dose-dependent QT prolongation with the use of citalopram as follows:

- with 20 mg citalopram, after 9 days, the maximum mean time-matched change in QTcF from baseline was 7.5 milliseconds (90% confidence interval 5.9–9.1 milliseconds)
- with 60 mg citalopram, the maximum mean time-matched change was 16.7 milliseconds (90% confidence interval 15–18.4 milliseconds).

There have also been rare reports of torsades de pointes with citalopram.

Given the above study results, the following changes to dose recommendations have been made.

- The recommended maximum daily dose of citalopram is now 40 mg.
- In people over 65 years of age, those with hepatic dysfunction, those taking medicines such as cimetidine or omeprazole which are known to inhibit the metabolism of citalopram, or those known to metabolise poorly via CYP2C19, the recommended maximum daily dose is now 20 mg.
- The recommended starting dose in the elderly is now 10 mg daily.

In addition, citalopram is now contraindicated in patients with congenital long QT syndrome.

Citalopram should be used with caution in patients at higher risk of developing prolongation of the QT interval, including those with:

- congestive heart failure
- bradyarrhythmias
- a predisposition to hypokalaemia or hypomagnesaemia
- concomitant medicines that prolong the QT interval.

There are also new monitoring recommendations for patients on citalopram:

- hypokalaemia and hypomagnesaemia should be corrected prior to initiation of treatment and potassium and magnesium levels should be periodically monitored
- more frequent ECG monitoring should be considered for patients at higher risk of QT prolongation.

Prescribers are reminded that suddenly stopping citalopram may cause withdrawal symptoms.

If citalopram is discontinued or the dose reduced, the patient should be monitored closely for the re-emergence or worsening of any symptoms of depression.

For full prescribing information, prescribers should refer to the Product Information, available from the TGA website.[1]

A similar study of escitalopram found much more limited dose-dependent QT prolongation. No changes to dosing recommendations for escitalopram have been made.

Clinicians are encouraged to report cases of QT prolongation with citalopram or other medicines, especially if extreme or associated with ventricular arrhythmias to the TGA.

REFERENCE

1. Cipramil Product Information. Lundbeck Australia Pty Ltd. 2011 Nov.

MEDICINES SAFETY UPDATE

Atomoxetine (Strattera) – risk of increased blood pressure and/or heart rate

The TGA is advising health professionals of important safety information regarding the risk of clinically significant increases in blood pressure and/or heart rate with the use of atomoxetine (Strattera).

This risk was identified from an analysis of combined data from clinical trials sponsored by atomoxetine's sponsor, Eli Lilly.

Health professionals are advised that atomoxetine is contraindicated in patients with symptomatic cardiovascular diseases, moderate to severe hypertension or severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced clinically important increases in blood pressure or heart rate.

Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease.

Atomoxetine should be used with caution in patients with, or with a family history of, congenital or acquired QT prolongation.

Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with atomoxetine and monitored during the course of treatment.

Heart rate and blood pressure should be measured in all patients before treatment with atomoxetine is started, after the dose is increased, and periodically during treatment to detect possible clinically important increases, particularly during the first few months of therapy.

The updated Product Information is available on the TGA website.

Health professionals are encouraged to report adverse reactions associated with atomoxetine to the TGA.

What to report? You don't need to be certain, just suspicious!

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

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

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

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

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

For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

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ARTICLE

Dangerous drugs online

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Key words
ecstasy, mephedrone, methylone, sibutramine

Aust Prescr 2012;35:32–5

SUMMARY

The risks associated with self-medication have been amplified by the ability to order prescription, non-prescription and complementary medicines online.

Products bought over the internet may be counterfeits or contain undeclared ingredients. Undeclared pharmaceuticals are increasingly being found in complementary medicines.

Marketing of medicines on the internet has not been limited to therapeutic drugs. There is a growing variety of new recreational or 'designer' drugs.

Without effective methods for detecting emerging drugs and with limited knowledge of their effects on users, online ordering presents a new challenge to public health.

Introduction

Prescription and non-prescription medicines can be bought legitimately online within Australia. Importation of prescription drugs into Australia is possible as long as regulatory requirements are met, although some internet transactions may involve counterfeits and fraud. Some of these products contain little, if any, active ingredient. In contrast 'herbal' and 'traditional' remedies or 'dietary supplements' sold over the internet may contain undeclared chemicals, prescription drugs or their analogues. The products most commonly marketed fraudulently on the internet include treatments for hair loss, impotence and obesity.

The Therapeutic Goods Administration (TGA) cannot test all the products on the Australian market, let alone the global range of products available online, to exclude all potentially harmful contaminants. Nonetheless, the TGA issued several alerts in 2011 for products containing undeclared drugs for the treatment of impotence.[1]

Weight loss products

The US Food and Drug Administration's (FDA) initiative against contaminated weight loss products revealed 72 products containing undeclared drugs and chemicals.[2] In most of them the undeclared active ingredient was sibutramine, a prescription-only medicine which was withdrawn from the Australian market in October 2010. Some of the products identified by the FDA recommended what equated to more than three times the recommended daily dosage of sibutramine, exposing consumers to an increased likelihood of serious adverse events.

The problem of contaminated products first came to the attention of our laboratory in 2008 following the admission of a patient to a psychiatric unit with drug-induced psychosis after taking slimming capsules. Withdrawal of the capsules produced a complete resolution of symptoms within several days. Subsequent testing of the capsules by gas chromatography mass spectroscopy detected the presence of sibutramine. Later that year another patient was admitted with florid psychosis following the use of a different brand of slimming capsule. Testing detected the primary urinary metabolite of sibutramine[3] and the capsules were found to contain the drug.

New recreational or 'designer' drugs

The ordering of drugs over the internet has not been limited to medicines. Substances can be produced to circumvent the laws defining illicit drugs.

Following a 'shortage' of ecstasy (3,4-methylenedioxymethamphetamine or MDMA), exploitation of loopholes in legislation permitted a rapid increase in the use of cathinone derivatives which are structurally similar to amphetamines. These substances are suspected in the deaths of up to 25 people in the UK and the class was banned there in 2010.[4] Of particular concern were mephedrone and methylone, analogues of methamphetamine and ecstasy which were already illegal in Australia. Mephedrone was the most popular 'legal' drug sold on the internet in Sweden until legislation was tightened.[4]

Naphyrone analogues, potent monoamine neurotransmitter reuptake inhibitors,[5] were also banned in the UK in 2010, but new psychoactive drugs continue to emerge. As these substances are less well known they are hard to identify and their effects are unpredictable.

Detection

Our laboratory's first encounter with novel designer drugs predated the use of the internet as an effective tool for their marketing. The epidemic of

ARTICLE

4-paramethoxyamphetamine (PMA) or 'death' related poisonings in South Australia in the 1990s was believed to be responsible for the deaths of up to 30 people.[6] Fortunately, the structure of PMA is similar to that of amphetamine so it is strongly crossreactive with the immunoassay screening methods used by most toxicology laboratories in Australia. Any re-emergence of this drug should be easily detected.

The structure of mephedrone and methylone sufficiently reduces their immunoreactivity, so drug testing may produce false negative results for sympathomimetics, even in overdose. The 2-aminoindane class of sympathomimetics may be sufficiently different structurally to evade not only detection but also the Australian legal description of analogues of controlled substances.

Conclusion

Many medical products are sold over the internet. Some of these products do not contain what the consumer expects. The internet may also be used to sell psychoactive substances with unpredictable effects.

Conflict of interest: none declared

See also page 29, Medicines Safety Update: *Caveat emptor* 'buyer beware' – the risks of purchasing unregistered medicines online.
Aust Prescr 2012;35:29.

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Book review

Therapeutic Guidelines: Neurology. Version 4.

Melbourne: Therapeutic Guidelines Limited; 2011. 242 pages.

Neurology is a highly specialised branch of medicine that never ceases to amaze with its clinical presentations. It has always had the potential to pose multiple clinical challenges to most practitioners. For these reasons, Therapeutic Guidelines: Neurology for me has proven to be the perfect mentor. The chapters provide clear, concise and evidence-based information on both the pharmacological and non-pharmacological management of neurological conditions encountered frequently in general practice.

'Getting to know your drugs' is a brief but complete summary of drugs used in neurology, with reliable information on the important drug interactions and precautions to be considered when treating patients. The appendices on monitoring antiepileptic drugs and sources of information are of great clinical value, as is the section on pregnancy and breastfeeding. Regular use of tables and flow charts makes it easy to read and user-friendly.

Therapeutic Guidelines: Neurology is the ultimate neurology reference tool. I recommend it for all medical practitioners, medical students and even allied health professionals, such as physiotherapists and occupational therapists, involved in the rehabilitation of patients with chronic neurological disease. All essential information required for a multidisciplinary and holistic approach to the management of patients is contained in this great resource.

Mohna Sharma
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Sydney

NEW DRUGS

New drugs

A

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

Prucalopride

Approved indication: constipation

Resotrans (Janssen-Cilag)

1 mg, 2 mg film-coated tablets

Australian Medicines Handbook section 12.4

Constipation sometimes does not respond to the usual treatments (see Managing constipation in adults, Aust Prescr 2010;33:116-9). Patients with an unsatisfactory response to laxatives can be considered for treatment with prucalopride.

Prucalopride is an agonist of the serotonin $5HT_4$ receptors. These receptors are found in the gut and stimulating them increases motility.

The drug is taken once a day. The tablets have a high oral bioavailability and can be taken with or without food. There is little metabolism of prucalopride. Most of the dose is excreted unchanged in the urine. A lower dose is recommended for elderly patients and those with severe renal or hepatic impairment. The half-life of prucalopride is one day.

The main double-blind clinical trials of prucalopride were carried out in the 1990s. Research into the product was temporarily suspended and the trials were not published until a decade later. The studies included three placebo-controlled trials with identical designs. They involved patients with a history of chronic constipation who had two or less bowel movements per week. These patients took prucalopride 2 mg or 4 mg, or placebo for 12 weeks. The primary efficacy endpoint in the trials was the proportion of patients who reported an average of three or more spontaneous bowel motions each week.[1,2,3]

The results (see Table) showed that more patients respond to prucalopride than to placebo, but the 4 mg dose is no better than the 2 mg dose. It is therefore the 2 mg dose which is approved for use in Australia.

During the trials the most frequent adverse effects seen with prucalopride were headache, nausea, abdominal pain and diarrhoea. Adverse events are more frequent at the start of treatment. The proportions of patients discontinuing treatment following adverse events were 1.9–6.7% with placebo, 4–8.2% with prucalopride 2 mg, and 6–15.1% with prucalopride 4 mg.[1,2,3] Adverse events also led to the withdrawal of 8% of the 1455 patients who continued to take (open-label) prucalopride after the main trials concluded.[4]

Cisapride and tegaserod were $5HT_4$ agonists that were removed from the market because of concerns about serious cardiovascular adverse effects. At present prucalopride does not appear to affect the QTc interval on the ECG or cause significant ischaemia. However, the product information advises caution if prescribing prucalopride for patients taking drugs which prolong the QTc interval.

Prucalopride is contraindicated in patients with ileus, obstruction or inflammatory bowel disease. It should not be used following bowel surgery.

As 86.6–90.8% of the trial participants were female,[1,2,3] the European regulatory agency approved prucalopride for use by women only. Women taking prucalopride must also use effective contraception as the drug is not recommended in pregnancy or breastfeeding. If prucalopride causes diarrhoea the efficacy of oral contraception may be reduced.

In Australia, prucalopride can be considered for adult men and women who have not responded to at least two laxatives for at least six months. Although some patients will respond to prucalopride, approximately 70% will not (Table). Consideration should be given to stopping prucalopride if it has not been effective after four weeks of treatment.

T T manufacturer provided additional useful information

Table **Response rates in trials of prucalopride**

TRIAL LOCATION	NUMBER OF PATIENTS	PLACEBO	PRUCALOPRIDE 2 MG	PRUCALOPRIDE 4 MG
USA[1]	620	12%	30.9%	28.4%
International[2]	713	9.6%	19.5%	23.6%
USA[3]	641	12.1%	23.9%	23.5%

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

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

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

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ANSWERS TO SELF-TEST QUESTIONS

1 True
2 True
3 True
4 True

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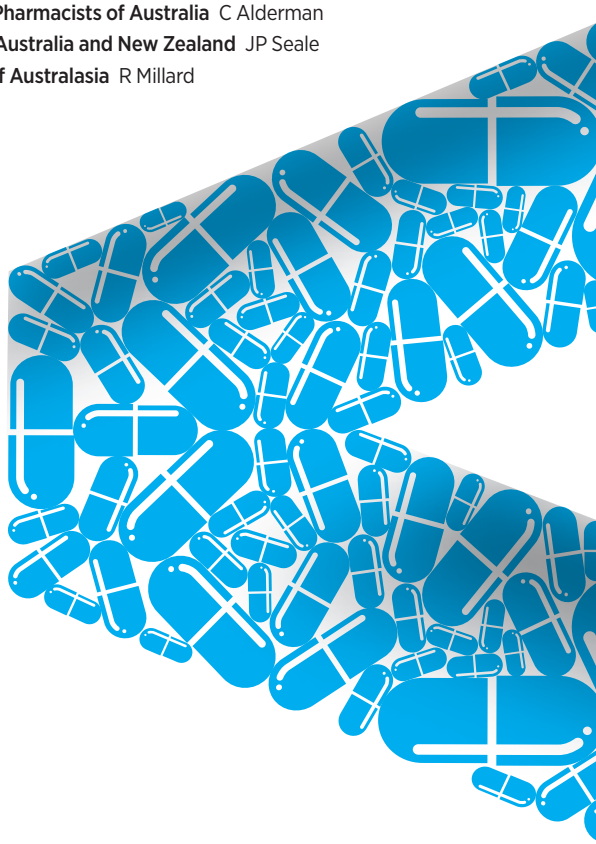

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