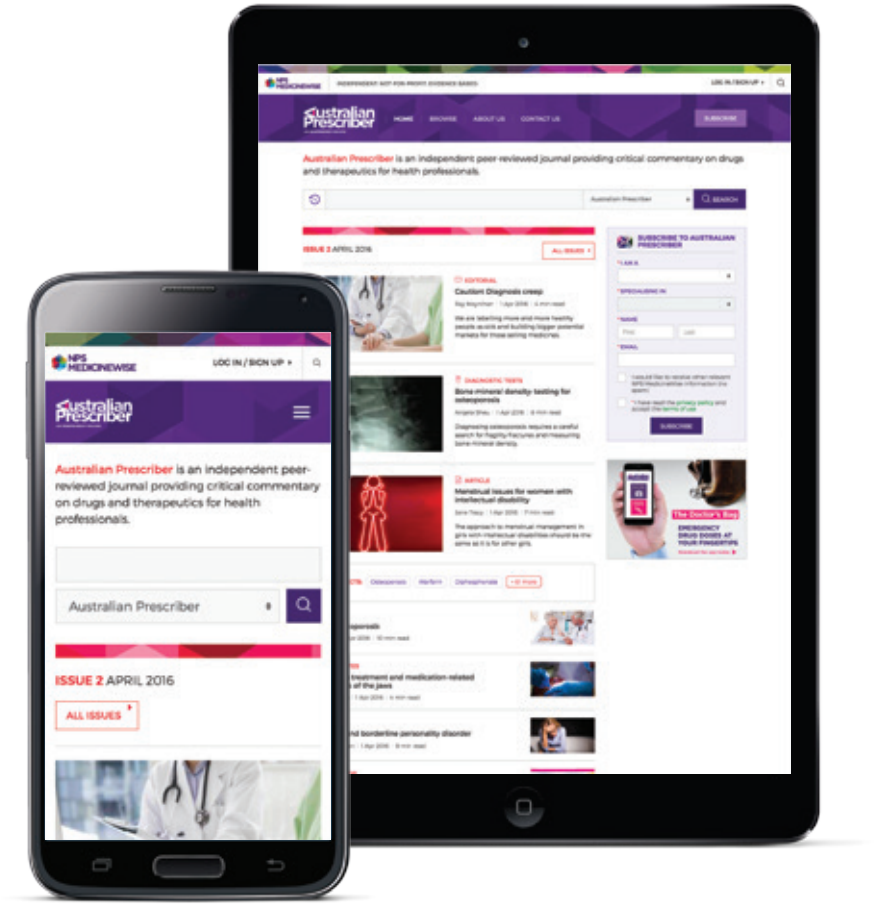
Australian Prescriber

AN INDEPENDENT REVIEW

June 2016
Volume 39 Number 3

nps.org.au/australianprescriber

THIS IS OUR LAST PRINT ISSUE



Subscribe for FREE to our digital edition.

nps.org.au/australianprescriber

NPS MEDICINEWISE

CONTENTS

EDITORIAL

The NPS MedicineWise vision for *Australian Prescriber*

Lynn Weekes AM
Chief executive officer
NPS MedicineWise
Sydney

Keywords
Australian Prescriber, medical journal

Aust Prescr 2016;39:70–1
http://dx.doi.org/10.18773/austprescr.2016.042

Australian Prescriber is much loved by you, its readers, and justifiably so. You have said in many readership surveys over the years that you value the quality of the content and the concise easy-to-read format. I know that you appreciate the 'without fear or favour' approach the journal takes, on both clinical and policy matters.

Some 53 000 health professionals receive *Australian Prescriber* including about 12 000 GPs, 9000 medical specialists and 14 000 pharmacists. It is popular internationally and the website has had a high rate of hits.

So why has NPS MedicineWise decided to make changes to this icon of Australian medical publishing and why now? It could be seen as a contentious decision and requires scrutiny because the future of *Australian Prescriber* is something we all care about. NPS MedicineWise has been the custodian of the journal since 2002 and we know it is one of our most valuable products.

At 40 years old, the journal remains as vital and effective as at inception. It has retained its relevance over the years by being connected with the readers, adapting to change and regularly introducing innovations. *Australian Prescriber* was one of the first Australian medical journals to go online. It was early to introduce mobile access and last year it produced its first app, The Doctor's Bag.

Australian Prescriber is run very efficiently by a small team of passionate and talented people. It has a thorough editorial process that adds tremendous value to the articles it commissions. It has strong and enduring relationships with some of the best medical and pharmacy minds in the country. I believe these three key components are critical to the quality, credibility and utility of *Australian Prescriber*. These are the things that I trust will never be compromised. However, maintenance of these critical features of *Australian Prescriber's* operations sits on a background of gradually increasing costs and a slightly smaller funding envelope for NPS MedicineWise in the coming years. We want to continue to innovate, grow the readership and keep pace with changes in medical publishing, and to succeed we need to reallocate resources.

On this basis, I have taken the decision to cease print publication and distribution. While I know many readers will miss the hard copy, I encourage you to tell us what formats will work best for you in a digital world. In 2012, doctors were spending an average of six hours per week online and had high levels of access to computers, tablets and smart phones.[1] An NPS MedicineWise survey in 2012 found that 55% of GPs prefer to do self-education online.[2] More recent data from the wider community would lead us to believe this connectivity has increased. A Nielson poll in December 2015 reported that over 18 million Australians use the internet. They spend 30 hours on average per week online and the growing areas of use are mobile phones and tablets, now making up 69% of all use.[3]

The future for *Australian Prescriber* is bright. It will remain an important medical journal here and internationally. One of the early challenges will be to increase email subscriptions to reach existing

From the Editor

After more than 40 years, this is the final print issue of *Australian Prescriber*.

When launching *Australian Prescriber* in 1975, the then Minister of Health said that the journal would aspire to fill a gap in the availability of balanced, impartial, reliable and up-to-date information. Nowadays people have access to so much information that there is a problem of information overload. To overcome this problem, Richard Day and Leone Snowden provide a list of useful sources of drug information.

The Editorial Executive Committee hopes the poster on swapping antidepressants will be another helpful resource. Nicholas Keks, Judy Hope and Simone Keogh explain the prescribing principles behind switching and stopping these drugs.

Compared to 1975, there are now many more medicines available and medical advances are producing innovative, but expensive, new drugs. Charles Denaro and Jennifer Martin consider the challenge of costly drugs.

Advances in technology also make it easier to investigate patients. While bone biopsy might have been used in 1975, Angela Sheu and Terry Diamond tell us that it is now rarely needed in the diagnosis of secondary osteoporosis.

Another challenge for today is the increase in the misuse of prescription drugs. Jenny James gives advice on dealing with drug-seeking behaviour.

As this edition is important in the history of *Australian Prescriber*, it is appropriate that Lynn Weekes explains her decision to stop print publication and to outline the vision for the journal within NPS MedicineWise. The end of print will also see the end of indexing. In addition to farewelling the staff at CanPrint Communications, the editorial team would like to thank Paul Hodgson who has indexed *Australian Prescriber* since 1992.

readers and also find new readers. For example, our circulation numbers show that not all GPs have signed up to receive *Australian Prescriber* in print. I hope we can move towards 100% of GPs reading the journal online.

Making the journal available when and how readers find most convenient is likely to mean expanding to some new media formats. The *Australian Prescriber* team will be undertaking evaluation to learn more about the best ways to bring digital content to you, whatever your needs.

There will be opportunities to bring articles together to support students and practitioners with particular questions or needs. The journal will also be looking for ways to support new prescribers, whatever their profession.

Australian Prescriber will continue to be essential reading for everyone wanting to stay up to date with drugs and therapeutics.

Conflict of interest: Lynn Weekes is the chief executive officer of NPS MedicineWise.

REFERENCES

1. Manhattan Research. Taking the Pulse Australia 2012. Burlington (MA): DRG; 2013 Feb 12. https://decisionresourcesgroup.com/report/4651 [cited 2016 May 1]
2. Yee M, Simpson-Young V, Paton R, Zuo Y. How do GPs want to learn in the digital era? Aust Fam Physician 2014;43:399-402.
3. Nielsen's Australian Online Landscape Review. Interactive and PDF - Dec 2015. Sydney: IAB Australia; 2016 Jan 19. www.iabaustralia.com.au/research-and-resources/research-resources/item/12-research-and-resource/2035-australian-online-landscape-review-interactive-and-pdf-dec-2015 [cited 2016 May 1]

The *Australian Prescriber* team for the final print issue

Back row, left to right:
Kathleen McGarry (Production coordinator),
Dr John Dowden (Editor),
Jennifer Dixon (Office administrator).

Front row:
Cherie Graham (Editorial assistant),
Dr Fiona Mackinnon (Deputy editor),
Georgina Hickey (Production manager).

EDITORIAL

The challenge of costly drugs

Charles Denaro
Director
Department of Internal Medicine and Aged Care
Royal Brisbane and Women's Hospital

Associate professor of Medicine
University of Queensland

Jennifer Martin
Chair of Clinical Pharmacology
University of Newcastle

Senior staff specialist
Calvary Mater Newcastle Hospital

Keywords
cost-effectiveness of drugs, hepatitis C, Pharmaceutical Benefits Scheme

Aust Prescr 2016;39:72–4
http://dx.doi.org/10.18773/austprescr.2016.037

From June 2005 to June 2014 the annual cost of the Pharmaceutical Benefits Scheme (PBS) rose from $6 billion to $9.15 billion. That is an increase of 52% or a growth rate of nearly 6% each year. At the same time the Highly Specialised Drugs and Section 100 programs of the PBS, which subsidise the most expensive drugs, increased by 200% or nearly 23% each year.[1] This growth has been largely driven by the arrival of expensive biological therapies, antiviral therapies for HIV and hepatitis C, and a variety of small molecules used to inhibit growth in subsets of various cancers. In Australia, enzyme replacement therapy for lysosomal storage diseases, funded by the separate Life Saving Drugs Program, can cost more than $200 000 per person, per year, for life. However, this therapy is not funded in New Zealand for Fabry disease, the commonest lysosomal storage disease.

In 2011 New Zealand paid less than half what Australia spent on medications per capita. This has been achieved by having a capped budget and competitive tendering.[2] In Australia there is a need to consider the fourth arm of the National Medicines Policy which aims to provide a consistent and supportive environment for the industry.[3]

The challenges are many, including knowing whether taxpayers are receiving value for money, funding treatments for our expanding ageing population, predicting long-term outcomes and cost-effectiveness for highly expensive medicines with inadequate long-term trial data. There are also the challenges in justifying extremely costly drugs for a few patients with a rare disease, and finding the funding while not reallocating resources from other areas of health care.

Many trials of costly drugs do not provide the information required to make a considered and accurate judgement of their value, particularly if registration or funding is based on phase II or observational data in small numbers of patients. Short-term surrogate end points for lifelong or life-threatening diseases also make the estimates of cost-effectiveness imprecise. For example, many expensive cancer therapies measure time to progression, but cannot quantify overall survival differences as patients in the control arm are often allowed to cross over to the active arm if the cancer progresses.[4] Treatments for rare diseases are a great development, but are also difficult to assess because the trials cannot recruit enough patients for long enough to show clear clinical end points. What is the true return on investment? What is lost if a new costly drug is approved? Can one make a considered value judgement if the median survival benefit is a couple of months?

A measure used in economic analysis is the quality-adjusted life-year (QALY). One QALY is one year of perfect health. QALYs can standardise the quality and quantity of life across diseases and populations. However they also have problems.[5] They are a relatively generic measure seen by some clinicians as lacking the specificity that is required in daily practice. In addition, the weighting system used to compute the QALY is most often calibrated in terms of social preferences sometimes derived in healthy populations rather than patients. Thus there is a reasonably valid belief that the value attached to quality of life may be determined by economists making deductions on assumptions that are not relevant to seriously ill patients.

Another challenge is to decide which patients will need treatment. Sofosbuvir is a new efficacious antiviral treatment for hepatitis C. However, it is very expensive, originally costing about US$84 000 for a 12-week course. Is it cost-effective to treat everyone when only a small percentage of patients with persistent hepatitis C infection will develop cirrhosis or hepatocellular cancer? The numbers in different studies vary – one cohort study in Germany followed 1980 women for 25 years. Overt cirrhosis developed in 0.5% and advanced fibrosis developed in 1.5%. Only one patient developed hepatocellular carcinoma.[6] After 35 years cirrhosis had only developed in 14% who remained viraemic. Despite these concerns the company marketing sofosbuvir recouped its initial outlay of US$11 billion (to buy this drug from a biotechnology company) in its first year of sales.[7] While there may be other benefits that are not yet studied or quantified, for example reduced infection risk and reduced general inflammatory symptoms such as fatigue, they come at a high price. Is it acceptable to delay treatment until the patent expires and generics become available? The benefits in terms of cost savings, and therefore the ability to make the drug available to wider populations as the evidence becomes available, could also be measurable.

The pharmaceutical industry is among the most profitable industries in the world.[7] While innovation and entrepreneurship must be encouraged, it is impossible to know exactly the cost to develop and bring a new drug to the market. Many breakthroughs have come from government-funded or university-funded basic research.[7] 'Big pharma' then brings the product to market. In fact pharmaceutical companies'

spending on sales and marketing dwarfs their investment in research and development outlays.

The way drugs are registered can influence their cost. Ranibizumab is approved for neovascular macular degeneration. However, it costs 40 times more than bevacizumab which is equally efficacious, but not approved for this indication.[8]

If only one supplier pays the Therapeutic Goods Administration (TGA) to evaluate an old, off-patent drug, it can charge a fortune if the drug is approved. For example, in 2003 thalidomide cost around $6 per capsule, but now costs approximately $30 per capsule.

The Pharmaceutical Benefits Advisory Committee (PBAC) has access to independent pharmacoeconomic expertise to assess submissions for including a drug on the PBS. However, many costly drugs only have a role in Australian public hospitals, and state governments do not fund comprehensive pharmacoeconomic assessments or even clinical pharmacologists for formulary decisions. Deciding whether to add a drug to a hospital formulary is thus problematic, especially as the funding must come out of a capped hospital budget, and relativity assessments such as QALYs are unable to guide decisions. Decisions across Australia are therefore haphazard and access to drugs may be determined by where the patient lives and the quality of the assessment by hospital formulary committees.

Drug companies are profit driven, while Australians are looking for the best value for money. What is the way forward?

Patents for some expensive biological therapies have expired or will expire in the near future. Biosimilars are mimic molecules of these therapies and potentially offer significant cost savings. However, they are not identical and require careful evaluation before marketing. Guidelines for biosimilar products have been produced.[9]

There is often much uncertainty about value for money, so post-marketing surveillance is required to assess important clinical outcomes. Unfortunately drug companies are less likely to fund expensive definitive trials once the drug is marketed. Funding for independent assessment is required. Drugs that do not realise their initial promise should be considered for removal from the PBS. Cinacalcet was removed from the PBS after reassessment of its cost-effectiveness.[10]

The TGA and the PBS charge applicants significant assessment fees and the legal liability for the drug once marketed in Australia remains with the applicant. The TGA and PBS should waive these fees in special circumstances to allow submissions from learned societies. Such circumstances should be limited to older drugs where the indication for their use is cost-effective compared to other drugs and where robust evidence for efficacy and safety exists. This would expedite the listing of new indications for current drugs (currently used off label) and have older, off-patent drugs listed and available. In this setting the liability incurred should rest with the Commonwealth. This would allow, for example, bevacizumab to be used for neovascular macular degeneration and diabetic retinopathy.

The cost of medicines may be influenced by factors such as international trade agreements, for example the Trans-Pacific Partnership.[11] There may need to be safeguards for patients and taxpayers if such agreements affect access to affordable drugs or delay the availability of generic or biosimilar drugs.[12]

An electronic national formulary for all Australian hospitals could be beneficial. It could be funded by the Commonwealth and updated regularly by a national formulary committee similar in structure to the PBAC. This would improve decision making and allow uniform access to efficacious and cost-effective drugs for all Australians irrespective of where they live. ◁

Conflict of interest: Charles Denaro is the Chair of the Queensland Health Medicines Advisory Committee. He currently serves on the Fabry Disease Advisory Boards for Genzyme and Shire, and was previously on the advisory boards of CSL and Menarini. He has received honoraria for speaking by Mundi Pharma and Shire, and was involved in a number of phase III trials for new oral anticoagulants – Bayer, Pfizer and Boehringer Ingelheim – and received sponsorship to attend conferences by Novartis, Sanofi, MSD, Vifor Pharma, Menarini and Astra Zeneca.

Conflict of interest: Jennifer Martin has been a member of the Pharmaceutical Benefits Advisory Committee and Queensland Health Medicines Advisory Committee. She is currently an Advisor to the Ministry of Health (New Zealand) Pharmacology and Therapeutic Advisory Committee and an external evaluator for the Therapeutic Goods Administration.

REFERENCES

1. The Pharmaceutical Benefits Scheme. PBS statistics. Canberra: Department of Health; 2015. www.pbs.gov.au/info/browse/statistics [cited 2016 May 1]
2. Babar Z, Vitry A. Differences in Australian and New Zealand medicines funding policies. Aust Prescr 2014;37:150-1. http://dx.doi.org/10.18773/austprescr.2014.059
3. National Medicines Policy 2000. Canberra: Department of Health and Ageing; 1999. www.health.gov.au/internet/main/publishing.nsf/Content/B2FFBF72029EEAC8CA257BF0001BAF3F/$File/NMP2000.pdf [cited 2016 May 1]

4. The Pharmaceutical Benefits Scheme. Crizotinib; 200 mg capsule, 60 and 250 mg capsule, 60; Xalkori. Canberra: Department of Health; 2015. www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-11/crizotinib-psd-11-2014 [cited 2016 May 1]
5. Kind P, Lafata JE, Matuszewski K, Raisch D. The use of QALYs in clinical and patient decision-making: issues and prospects. Value Health 2009;12 Suppl 1:S27-S30. http://dx.doi.org/10.1111/j.1524-4733.2009.00519.x
6. Wiese M, Grüngreiff K, Güthoff W, Lafrenz M, Oesen U, Porst H; East German Hepatitis C Study Group. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany--a 25-year multicenter study. J Hepatol 2005;43:590-8. http://dx.doi.org/10.1016/j.jhep.2005.04.007
7. Avorn J. The $2.6 billion pill--methodologic and policy considerations. N Engl J Med 2015;372:1877-9. http://dx.doi.org/10.1056/NEJMp1500848
8. Harvey KJ, Day RO, Campbell WG, Lipworth W. Saving money on the PBS: ranibizumab or bevacizumab for neovascular macular degeneration? Med J Aust 2011;194:567-8.
9. Council of Australian Therapeutic Advisory Groups. Overseeing biosimilar use: guiding principles for the governance of biological and biosimilar medicines in Australian hospitals. Sydney: CATAG; 2015. www.catag.org.au/resources [cited 2016 May 1]
10. Sensipar (cinacalcet) PBS listing to be deleted. NPS RADAR 2015 April. www.nps.org.au/publications/health-professional/nps-radar/2015/april-2015/brief-item-sensipar [cited 2016 May 1]
11. Trans-Pacific Partnership Agreement. Canberra: Department of Foreign Affairs and Trade; 2016. http://dfat.gov.au/trade/agreements/tpp/Pages/trans-pacific-partnership-agreement-tpp.aspx [cited 2016 May 1]
12. Thow AM, Gleeson DH, Friel S. What doctors should know about the Trans-Pacific Partnership Agreement. Med J Aust 2015;202:165-6. http://dx.doi.org/10.5694/mja14.01714

Letters to the Editor

Metformin and patients on dialysis

Aust Prescr 2016;39:74–5
http://dx.doi.org/10.18773/austprescr.2016.041

I enjoyed reading the concise, well-referenced summary on prescribing for patients on dialysis.[1] However, the statement 'Metformin is contraindicated due to the risk of lactic acidosis' is not referenced and is perhaps not supported by the available evidence.

A Cochrane review on the risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes concluded that there is no evidence at present that metformin is associated with an increased risk for lactic acidosis when prescribed under the study conditions.[2] The authors commented that of the 334 prospective studies, 143 (53%) allowed for the inclusion of renal insufficiency, following 37 360 patient-years of metformin use. One trial in the review questioned the standard contraindications by studying 393 patients, all with at least one contraindication to metformin use, and found no cases of lactic acidosis over four years.[3] All of the patients had renal insufficiency, with mean plasma creatinine concentrations of 1.5–2.5 mg/dL (mean 1.8 mg/dL).

A review of metformin in chronic kidney disease nicely summarises the issue.[4] It cites two small studies of metformin use in dialysis patients and recommends 250 mg daily for peritoneal dialysis patients and 500 mg after each dialysis session for those receiving haemodialysis.

Metformin is renally excreted and in overdose has been seen to cause lactic acidosis without other contributory comorbidity. While there are grounds for caution in patients on dialysis, an increased risk of lactic acidosis has not been specifically established. Many renal physicians choose to administer metformin in reduced doses to selected patients with end-stage renal disease because of its proven efficacy in the management of overweight patients with type 2 diabetes.

Stephen Richards
Renal physician
Perth

REFERENCES

1. Smyth B, Jones C, Saunders J. Prescribing for patients on dialysis. Aust Prescr 2016;39:21-4. http://dx.doi.org/10.18773/austprescr.2016.008
2. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010:CD002967. http://dx.doi.org/10.1002/14651858.CD002967.pub4
3. Rachmani R, Slavachevski I, Levi Z, Zadok B, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. Eur J Intern Med 2002;13:428-33. http://dx.doi.org/10.1016/S0953-6205(02)00131-0
4. Heaf J. Metformin in chronic kidney disease: time for a rethink. Perit Dial Int 2014;34:353-7. http://dx.doi.org/10.3747/pdi.2013.00344

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. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Brendan Smyth, Ceridwen Jones and John Saunders, the authors of the article, comment:

We thank Dr Richards for his comments which highlight the growing interest in extending the use of metformin to patients with moderate to severe chronic kidney disease. Within the constraints of our brief review we preferred to adhere to a conservative recommendation regarding metformin use in end-stage renal disease without describing the current controversy. We agree that recent studies have substantially altered our understanding of the risk–benefit profile of metformin in patients with chronic kidney disease and we look forward to larger studies with substantial follow-up of safety end points. However, until these are available we would continue to suggest that metformin not be used in dialysis patients except under the close supervision of a nephrologist or as part of a clinical trial.

Anal fissures and liquid paraffin

Aust Prescr 2016;39:75
http://dx.doi.org/10.18773/austprescr.2016.040

Congratulations on the concise article on anal fissure.[1] It covered pathology and management well with one exception, the role of stool softening.

While the cause of an anal fissure is unknown, the condition is perpetuated by the cycle:

> pain → internal sphincter spasm → faecal retention → hard stool → rapid anal stretching at (inevitable) defaecation → opening of the fissure → pain

This cycle can be broken by adequate stool softening. Increasing fibre intake is slow to act and often fails to give adequate softening. The stool needs to be as soft as toothpaste.

Osmotic agents (e.g. macrogol) or non-absorbed sugars (e.g. lactulose) can be used but have their disadvantages. The cheapest, most rapid acting product is liquid paraffin. A large dose can be given initially so that within 24 hours defaecation is pain free or almost so. In children, depending on their age, a dose of 20–30 mL to start can be followed by 10–15 mL twice daily. The dose can be easily adjusted according to the response. Liquid paraffin can be continued for two to three months, after which it is reduced slowly. Fibre can then be used if hard stools are a long-term problem.

As paraffin is not digested, does not change intestinal movement, and does not cause movement of water in or out of the gut, it is relatively safe. Some leaking of oil is seen occasionally but this can be controlled by lowering the dose by a few mL.

I have yet to find good evidence of a complication other than pulmonary aspiration secondary to gastro-oesophageal reflux. It is best to avoid giving a dose last thing at night. Macrophages in intestinal nodes can show micro droplets but no ill effect has been noted. About 30 years ago there was a belief that liquid paraffin could cause fat soluble vitamin deficiency, however this has not been substantiated by subsequent research.[2]

Hugh Martin
Paediatric surgeon
Sydney

REFERENCE

1. Schlichtemeier S, Engel A. Anal fissure. Aust Prescr 2016;39:14-7. http://dx.doi.org/10.18773/austprescr.2016.007
2. Sharif F, Crushell E, O'Driscoll K, Bourke B. Liquid paraffin: a reappraisal of its role in the treatment of constipation. Arch Dis Child 2001;85:121-4. http://dx.doi.org/10.1136/adc.85.2.121

Steven Schlichtemeier and Alexander Engel, the authors of the article, comment:

We thank Dr Martin for his response detailing the use of liquid paraffin as part of the conservative management of patients with acute anal fissures. We agree that increased fibre intake may not provide adequate stool softening and often an additional or alternate agent may be necessary to achieve adequate stool consistency. Its effectiveness, cost and low adverse-effect profile may make liquid paraffin the product of choice in this situation. It may even be the preferred agent to begin with in children as a small amount of liquid may be favoured over spoonfuls of fibre.

Unfortunately, most studies combine increased fibre and laxatives with sitz baths as part of best supportive management in comparison to topical treatment, botulinum injections or surgery. There is no good-quality evidence comparing increased fibre to the different classes of laxatives in the management of anal fissures. However, stool softeners may benefit the patient without the need for a drug, injection or surgery.

ARTICLE

Switching and stopping antidepressants

Nicholas Keks
Director[1]
Adjunct professor[2]
Judy Hope
Deputy director[1]
Senior lecturer[2]
Simone Keogh
Psychiatrist and senior fellow[1]

[1] Centre for Mental Health Education and Research Delmont Private Hospital
[2] Monash University Melbourne

Keywords
antidepressant, drug interaction, drug withdrawal, serotonin syndrome

Aust Prescr 2016;39:76–83
http://dx.doi.org/10.18773/austprescr.2016.039

SUMMARY

Switching from one antidepressant to another is frequently indicated due to an inadequate treatment response or unacceptable adverse effects. All antidepressant switches must be carried out cautiously and under close observation.

Conservative switching strategies involve gradually tapering the first antidepressant followed by an adequate washout period before the new antidepressant is started. This can take a long time and include periods of no treatment with the risk of potentially life-threatening exacerbations of illness.

Clinical expertise is needed for more rapid or cross-taper switching as drug toxicity, including serotonin syndrome, may result from inappropriate co-administration of antidepressants. Some antidepressants must not be combined.

Antidepressants can cause withdrawal syndromes if discontinued abruptly after prolonged use. Relapse and exacerbation of depression can also occur. Gradual dose reduction over days to weeks reduces the risk and severity of complications.

Introduction

Antidepressant drugs are indicated for the treatment of depression, anxiety disorders (including panic and social phobia), obsessive compulsive disorder and post-traumatic stress disorder. There are over 20 antidepressants currently available in Australia. These can be divided into 13 clinically relevant groups, which differ substantially in their pharmacodynamic and pharmacokinetic characteristics.

Up to two-thirds of patients with major depression fail to respond to their first antidepressant drug. After assuring correct diagnosis, optimal dose, duration and adherence to treatment, a change of antidepressant drug is indicated.[1] A patient is unlikely to respond if there has been no improvement after three to four weeks on an adequate dose of antidepressant.[2] About a quarter of patients switched to a second antidepressant can be expected to achieve remission.[3] There is no evidence that switching between classes of antidepressants is more effective than switching within a class.[4] Unacceptable adverse effects from antidepressants, such as sexual dysfunction and weight gain, may also necessitate a change of therapy.[5] Switching from one antidepressant to another is a common clinical challenge.

Withdrawal of an antidepressant is also indicated after an episode of depression has been adequately treated – usually six to nine months after recovery from a single episode. Serious physical illness, pregnancy and surgery may also be reasons for stopping antidepressant therapy. Up to a third of patients stop antidepressants soon after starting and many more only partially adhere to treatment.[6]

Withdrawing antidepressants

If used for longer than six weeks, all antidepressants have the potential to cause withdrawal syndromes if they are stopped or rapidly reduced (with the possible exception of agomelatine). As a result many patients believe that antidepressants are addictive. This is not the case as abusive and compulsive use, tolerance and drug seeking do not occur with antidepressant drugs. Withdrawal syndromes occur with many drugs (such as corticosteroids) when used long term.

The usual recommended period for antidepressant dose reduction is a minimum of four weeks.[2] However, abrupt cessation may at times be unavoidable on clinical grounds. The time frame for dose reduction also depends on individual risk for withdrawal symptoms, patient preference and experience during withdrawal, and drug characteristics such as half-life (Table 1).

Previous withdrawal symptoms and anxiety when starting antidepressant treatment are predictors of future discontinuation problems. Some patients experience little discomfort despite abrupt cessation, while others are severely affected. In a minority, withdrawal symptoms are not diminished by extending the duration of dose taper. These patients may prefer rapid cessation and a briefer withdrawal period. Many will not experience symptoms in the early part of withdrawal (which could proceed more rapidly) but develop severe symptoms in the

later stages (when dose reduction may need to be more gradual).

Withdrawal symptoms

Withdrawal symptoms generally begin within hours to days of dose reduction, depending on the characteristics of the particular drug.[7] Withdrawing selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) tends to cause flu-like symptoms, nausea, lethargy, dizziness, ataxia, 'electric shock' sensations, anxiety, irritability, insomnia and vivid dreams. The symptoms can be extremely disabling for some patients.

Venlafaxine is associated with the most severe withdrawal effects. Paroxetine is also troublesome while fluoxetine rarely causes withdrawal symptoms (especially if the dose is under 40 mg) due to the long half-life of the parent drug and its active metabolite (about 7 days). Withdrawal of tricyclic antidepressants can cause nausea, headache, abdominal pain, diarrhoea, lethargy, anxiety, insomnia and vivid dreams. It is unlikely that withdrawal symptoms will occur after cessation of low-dose tricyclics used in pain treatment. Withdrawing irreversible monoamine oxidase inhibitors such as tranylcypromine is particularly troublesome. It often causes agitation, irritability, mood disorders, dreams, cognitive impairment and occasionally psychosis and delirium.

Relapse and exacerbation

Stopping antidepressants can also result in relapse or exacerbation of the psychiatric illness. Relapse of depressive symptoms (including suicidal ideation and self-harm) and recurrence of panic attacks and severe anxiety can all occur with dose reduction and cessation. Such exacerbations can cause life-threatening behaviours in high-risk patients, and antidepressant withdrawal must be a carefully considered decision made by the well-informed patient, often their family, and the prescriber. Avoid stopping an antidepressant abruptly – withdrawal over weeks to months (if possible) reduces the risk of relapse.[2]

Switching strategies

A number of strategies are available for switching between antidepressants (Table 2).[6,8] Close clinical observation and caution is required with all approaches, as some patients may respond idiosyncratically and serious complications can occur. Individual patient factors and illness factors may require considerable modification of a switching strategy.

The most conservative strategy, with the lowest risk of drug interactions, is to gradually taper the dose of the first antidepressant to minimise withdrawal symptoms then start a washout period equivalent to five half-lives of the drug (Table 1). This does not apply to irreversible monoamine oxidase inhibitors where a specified long period of washout is mandatory (see Table 3). Five half-lives equates to about five days for most SSRIs except fluoxetine, which can still be significantly active five or more weeks after cessation. The second antidepressant is then introduced according to the starting dose recommendations.

Table 1 **Approximate half-lives of antidepressants**

Antidepressant	Approximate half-life (days)
citalopram	1.5
escitalopram	1.5
paroxetine	1.0
sertraline	1.1–1.3
fluoxetine	4–16*
fluvoxamine	0.6
vortioxetine	2.4–2.8
agomelatine	0.04–0.08
desvenlafaxine	0.4
duloxetine	0.5
venlafaxine	0.6†
mianserin	0.9–2.5
mirtazepine	0.8–1.6‡
reboxetine	0.5
amitriptyline	0.2–1.9
imipramine	0.2–1.3
nortriptyline	0.8–2.3
doxepin	0.4–1.0
dothiepin	2.1
trimipramine	0.6–1.6
clomipramine	0.6–2.5
moclobemide	0.08
phenelzine	see below§
tranylcypromine	see below§

* fluoxetine plus active metabolite norfluoxetine
† venlafaxine plus active metabolite desvenlafaxine
‡ a longer half-life (up to 65 hours) has occasionally been recorded and a shorter half-life is sometimes seen in young men
§ biological activity persists for 14–21 days

The dose is usually tapered over four weeks, similar to the minimum period required for antidepressant discontinuation. However, the time frame may need to be modified depending on patient factors.

As the conservative switch can take quite a long time and usually includes at least several days where the patient is not on an antidepressant, a compromise strategy is the moderate switch. Here the washout period can generally be shortened to about two days. The risk of drug interactions is increased with this approach, but is still quite low. The conservative and moderate switch techniques are both suitable for general practice.

Direct and cross-taper switch methods can also be used but considerable expertise is necessary (Table 2). Some patients will require admission to hospital. A direct switch – one drug is stopped and another drug is commenced the next day at the usual therapeutic dose – can be used when switching between some SSRIs, SNRIs and tricyclic antidepressants. However, there will be a considerable risk of withdrawal symptoms and drug interactions. A cross-taper strategy, where the first antidepressant dose is reduced while the second antidepressant is introduced at a low dose and gradually increased, can be done safely with only some antidepressants (Table 3).

Switching between specific antidepressants

Table 3 lists generalised guidelines for switching patients from one antidepressant to another.[2, 8-10] The recommendations are applicable to any switching strategy. Circumstances where only a conservative strategy can be used are identified. Table 3 also states when antidepressants should not be co-administered or tapered at the same time.

Serotonin syndrome

As many antidepressants have serotonergic activity, serotonin syndrome can occur during antidepressant switching. While the syndrome may cause mild

Table 2 **Techniques for switching from one antidepressant to another** [6]

Method	Comment
Conservative switch: • the first antidepressant is gradually reduced and stopped • there follows a drug-free washout interval of five half-lives of the first antidepressant • the new antidepressant is started according to its dose recommendation	Most appropriate for general practice. The risk of drug interactions is very low but discontinuation symptoms may occur.
Moderate switch: • the first antidepressant is gradually reduced and stopped • there follows a drug-free washout interval of 2–4 days • the new antidepressant is started at a low dose	Also recommended for use in general practice. The risk of drug interactions is low but discontinuation symptoms may occur.
Direct switch: • the first antidepressant is stopped • the second antidepressant is started the next day at the usual therapeutic dose	Quick and simple but discontinuation symptoms are likely depending on the second antidepressant. The risk of drug interactions is substantial, depending on the second antidepressant. Method requires clinical expertise and is only feasible in selected instances, such as swapping from one short half-life SSRI to another.
Cross-taper switch: • the first antidepressant is gradually reduced and stopped • the second antidepressant is introduced at a low dose at some stage during the reduction of the first antidepressant, so that the patient is taking both antidepressants simultaneously • the dose of the second antidepressant is increased to the therapeutic dose when the first antidepressant has been stopped	Frequently used for patients with high risk from illness relapse but there is risk of drug interactions and increased adverse effects from combined medications. Only feasible in selected instances. Requires clinical expertise.

Note: Above strategies do not apply to monamine oxidase inhibitors, for which strict recommendations must be followed (Table 3)

SSRI selective serotonin reuptake inhibitor

Adapted from reference 6

symptoms such as nervousness, agitation, tremor, diaphoresis, shivering, mydriasis, hyperreflexia and diarrhoea, in more severe cases tachycardia, hyperthermia, hypertension, myoclonus, muscular rigidity and delirium can occur. Convulsions, organ system failure and death may follow. Prevention through minimising interactions between potent serotonergic drugs is critical.[11]

The only significant interaction for agomelatine is with fluvoxamine (Table 3). Vortioxetine (an SSRI with possible other serotonergic effects) can interact with a variety of antidepressants. Caution is required for switching and the prescriber should consult relevant drug information before proceeding. The same caution applies to duloxetine (Table 3).

Fluoxetine is a particular challenge for switching because of its long half-life. Serotonin syndrome can occur if clomipramine, fluvoxamine or monoamine oxidase inhibitors are introduced before an adequate washout of fluoxetine, which can take five or more weeks. Tricyclic antidepressants can be introduced at a low dose after fluoxetine withdrawal. However, the low dose needs to be continued for several weeks to avoid cardiotoxic plasma concentrations of tricyclic antidepressant due to inhibition of tricyclic antidepressant metabolism by fluoxetine. Early signs of tricyclic antidepressant toxicity include drowsiness, tachycardia and postural hypotension.

When changing from irreversible monoamine oxidase inhibitors (phenelzine and tranylcypromine) to all other antidepressants, with the possible exception of agomelatine, an adequate washout of two to three weeks is mandatory.

Conclusion

Switching antidepressants involves drug cessation, which may cause withdrawal symptoms and relapse or exacerbation of the psychiatric illness. Gradual antidepressant withdrawal reduces the risk of complications. If the washout period is not long enough (defined by half-life of the drug), introducing a new antidepressant can cause drug interactions leading to toxicity, particularly serotonin syndrome. Switching from one antidepressant to another requires careful observation and caution. ◁

Conflict of interest: none declared

REFERENCES

1. Little A. Treatment-resistant depression. Am Fam Physician 2009;80:167-72.
2. Taylor D, Paton C, Kapur S, editors. The Maudsley prescribing guidelines in psychiatry. 11th ed. London: Wiley Blackwell; 2015.
3. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17. http://dx.doi.org/10.1176/ajp.2006.163.11.1905
4. Souery D, Serretti A, Calati R, Oswald P, Massat I, Konstantinidis A, et al. Switching antidepressant class does not improve response or remission in treatment-resistant depression. J Clin Psychopharmacol 2011;31:512-6. http://dx.doi.org/10.1097/JCP.0b013e3182228619
5. Keks NA, Hope J, Culhane C. Management of antidepressant-induced sexual dysfunction. Australas Psychiatry 2014;22:525-8. http://dx.doi.org/10.1177/1039856214556323
6. Jefferson JW. Strategies for switching antidepressants to achieve maximum efficacy. J Clin Psychiatry 2008;69 Suppl E1:14-8.
7. Schweitzer I, Maguire K. Stopping antidepressants. Aust Prescr 2001;24:13-5. http://dx.doi.org/10.18773/austprescr.2001.008
8. Luft B. Antidepressant switching strategies. Graylands Hospital Drug Bulletin 2013;20:1-4.
9. Psychotropic Expert Group. Therapeutic Guidelines: psychotropic. Version 7. Melbourne: Therapeutic Guidelines Limited; 2013.
10. Procyshyn RM, Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Clinical handbook of psychotropic drugs. 21st ed. Boston: Hogrefe Publishing; 2015.
11. Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. BMJ 2014;348:g1626. http://dx.doi.org/10.1136/bmj.g1626

FURTHER READING

Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. Psychother Psychosom 2015;84:72-81. http://dx.doi.org/10.1159/000370338

Table 3 **Guidelines for switching between specific antidepressants** [2,8-10]

↓FROM / TO→	**citalopram escitalopram paroxetine sertraline (SSRIs)**	**fluoxetine**	**fluvoxamine**	**vortioxetine**	**agomelatine**	**desvenlafaxine duloxetine venlafaxine (SNRIs)**
citalopram escitalopram paroxetine sertraline (SSRIs)	taper drug, start alternative SSRI at low dose*	taper and stop drug, then start fluoxetine at 10 mg§	taper and stop drug, then start fluvoxamine at 50 mg§	taper drug, start vortioxetine at 5 mg*	taper drug, start agomelatine*	taper drug, then start SNRI at low dose*
fluoxetine	stop fluoxetine (or taper if dose >40 mg/day), wait 7 days for washout, then start above SSRI at low dose†§		stop fluoxetine (or taper if dose >40 mg/day), wait 14 days for washout, then start fluvoxamine at 50 mg†§	stop fluoxetine (or taper if dose >40 mg/day), wait 7 days for washout, then start vortioxetine at 5 mg†§	stop fluoxetine (or taper if dose >40 mg/day), start agomelatine	taper and stop fluoxetine, wait 7 days for washout, then start SNRI at low dose†§
fluvoxamine	taper and stop fluvoxamine, then start above SSRI at low dose§	taper and stop fluvoxamine, then start fluoxetine at 10 mg§		taper and stop fluvoxamine, start vortioxetine at 5 mg§	taper and stop fluvoxamine, wait 7 days for washout, then start agomelatine§	taper and stop fluvoxamine, then start SNRI at low dose§
vortioxetine	taper vortioxetine, start above SSRI at low dose*	taper and stop vortioxetine, start fluoxetine at 10 mg§	taper and stop vortioxetine, start fluvoxamine at 50 mg§		taper vortioxetine, start agomelatine at 25 mg*	taper vortioxetine, start SNRI at low dose*
agomelatine	stop agomelatine, then start above SSRI	stop agomelatine, then start fluoxetine	stop agomelatine, then start fluvoxamine*	stop agomelatine, then start vortioxetine		stop agomelatine, then start SNRI
desvenlafaxine duloxetine venlafaxine (SNRIs)	taper SNRI, start above SSRI at low dose*	taper and stop SNRI, start fluoxetine at 10 mg§	taper and stop SNRI, start fluvoxamine at 50 mg§	taper SNRI, start vortioxetine at 5 mg*	taper SNRI, start agomelatine*	taper SNRI, start alternative SNRI at low dose*
mianserin mirtazepine	taper drug, start above SSRI*	taper drug, start fluoxetine*	taper drug, start fluvoxamine*	taper drug, start vortioxetine*	taper drug, start agomelatine*	taper drug, start SNRI*
reboxetine	taper reboxetine, start above SSRI*	taper reboxetine, start fluoxetine*	taper reboxetine, start fluvoxamine at 50 mg*	taper reboxetine, start vortioxetine at 5 mg*	taper reboxetine, start agomelatine*	taper reboxetine, start SNRI at low dose*

mianserin mirtazapine	reboxetine	amitriptyline imipramine nortriptyline doxepin dothiepin trimipramine (TCAs)	clomipramine	moclobemide	phenelzine tranylcypromine (MAOIs)
taper drug, then start above drug at low dose*	taper drug, start reboxetine*	taper SSRI, start above drug at low dose (usually 25 mg)*	taper and stop drug, then start clomipramine at 25 mg§	taper and stop drug for 7 days washout before starting moclobemide at low dose§	taper and stop drug for 7 days washout before starting MAOI at low dose§
stop fluoxetine (or taper if dose >40 mg/day), start above drug at low dose	stop fluoxetine (or taper if dose >40 mg/day), start reboxetine at 4 mg	stop fluoxetine (or taper if dose >40 mg/day), wait 14 days for washout, then start above drug at 25 mg and continue low dose for further 3 weeks‡	stop fluoxetine (or taper if dose >40 mg/day), wait 14 days for washout, then start clomipramine at 25 mg and continue this dose for further 3 weeks‡	stop fluoxetine (or taper if dose >40 mg/day), then wait 5–6 weeks for washout before cautiously commencing low-dose moclobemide§	stop fluoxetine (or taper if dose >40 mg/day), then wait 5–6 weeks for washout before cautiously commencing low-dose MAOI§
taper and stop fluvoxamine, then start above drug at low dose§	taper fluvoxamine, start reboxetine at 4 mg*	taper fluvoxamine, start above drug at 25 mg*	taper and stop fluvoxamine, start clomipramine at 25 mg§	taper and stop fluvoxamine, wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop fluvoxamine, wait 7 days for washout before cautiously commencing low-dose MAOI§
taper vortioxetine, start above drug at low dose*	taper vortioxetine, start reboxetine*	taper vortioxetine, start above drug at low dose (usually 25 mg)*	taper and stop vortioxetine, start clomipramine at 25 mg§	taper and stop vortioxetine for 14 days washout before starting moclobemide at low dose§	taper and stop vortioxetine for 21 days washout before starting MAOI at low dose cautiously§
stop agomelatine, then start above drug	stop agomelatine, then start reboxetine	stop agomelatine, then start above drug at low dose (usually 25 mg)*	stop agomelatine, then start clomipramine	stop agomelatine, then start moclobemide	stop agomelatine, then start MAOI
taper SNRI, start above drug at low dose*	taper SNRI, start reboxetine at 4 mg*	taper SNRI, start above drug at 25 mg*	taper SNRI, start clomipramine at 25 mg*	taper and stop SNRI, wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop SNRI, wait 7 days for washout before cautiously commencing low-dose MAOI§
taper drug, start drug above at low dose*	taper drug, start reboxetine at 4 mg*	taper drug, start above drug at 25 mg*	taper drug, start clomipramine at 25 mg*	taper and stop drug, wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop drug, wait 14 days for washout before cautiously commencing low-dose MAOI§
taper reboxetine, start above drug*		taper reboxetine, start above drug at 25 mg*	taper reboxetine, start clomipramine at 25 mg*	taper and stop reboxetine, then wait 7 days for washout before cautiously commencing low-dose moclobemide§	taper and stop reboxetine, then wait 7 days for washout before cautiously commencing low-dose MAOI§

Table 3 **Guidelines for switching between specific antidepressants [2,8-10] (continued)**

↓FROM / TO→	**citalopram escitalopram paroxetine sertraline (SSRIs)**	**fluoxetine**	**fluvoxamine**	**vortioxetine**	**agomelatine**	**desvenlafaxine duloxetine venlafaxine (SNRIs)**
amitriptyline imipramine nortriptyline doxepin dothiepin trimipramine (TCAs)	taper first drug and start above drug at low dose*	taper and stop first drug before starting fluoxetine§	taper drug, start fluvoxamine at 50 mg*	taper drug, start vortioxetine at 5 mg*	taper drug, start agomelatine*	taper drug, start SNRI at low dose*
clomipramine	taper and stop clomipramine, then start above SSRI at low dose§	taper and stop clomipramine, then start fluoxetine at 10 mg§	taper and stop clomipramine, then start fluvoxamine at 50 mg§	taper and stop clomipramine, then start vortioxetine at 5 mg§	taper clomipramine, start agomelatine*	taper and stop clomipramine, then start SNRI at low dose§
moclobemide	taper and stop moclobemide, then wait 24 hours for washout before starting above drug§	taper and stop moclobemide, then wait 24 hours for washout before starting fluoxetine§	taper and stop moclobemide, then wait 24 hours for washout before starting fluvoxamine§	taper and stop moclobemide, then wait 24 hours for washout before starting vortioxetine§	taper moclobemide, start agomelatine	taper and stop moclobemide, then wait 24 hours for washout before starting SNRI§
phenelzine tranylcypromine (MAOIs)	taper and stop MAOI, then wait 14 days for washout before starting above drug§	taper and stop MAOI, then wait 14 days for washout before starting fluoxetine§	taper and stop MAOI, then wait 14 days for washout before starting fluvoxamine§	taper and stop MAOI, then wait 14 days for washout before starting vortioxetine§	taper and stop MAOI, start agomelatine*	taper and stop MAOI, then wait 14 days for washout before starting SNRI§

Taper means gradual dose reduction, with lowering by increments every few days, usually over a period of 4 weeks, modified by patient experience, drug, illness and other factors.

All switches from one antidepressant to another may result in serious complications. Switches must be undertaken cautiously and under close observation.

The recommendations in this table are based on clinical experience, product information, empirical evidence and recommendations from other guidelines. It may be necessary to modify the switching process depending on patient, illness and interacting drug variables, determined by the patient's clinical progress. In appropriate circumstances expert prescribers may use less conservative switch strategies if justified by harm–benefit considerations arising from factors such as illness severity.

MAOI monoamine oxidase inhibitor
SNRI serotonin noradrenaline reuptake inhibitor
TCA tricyclic antidepressant
SSRI selective serotonin reuptake inhibitor

An enlarged poster version of this Switching-antidepressants table has been inserted in the current issue of *Australian Prescriber*. Extra copies are available on request.

mianserin mirtazapine	reboxetine	amitriptyline imipramine nortriptyline doxepin dothiepin trimipramine (TCAs)	clomipramine	moclobemide	phenelzine tranylcypromine (MAOIs)
taper drug, start above drug at low dose*	taper drug, start reboxetine at 4 mg*	taper first drug, start alternative TCA at 25 mg*	taper drug, start clomipramine cautiously at 25 mg*	taper and stop drug, then wait 7 days for washout before starting moclobemide§	taper and stop drug, then wait 14 days (21 days for imipramine) before starting MAOI§
taper clomipramine, then start above drug at low dose*	taper clomipramine, then start reboxetine at 4 mg*	taper clomipramine, then start drug at 25 mg*		taper and stop clomipramine, then wait 7 days for washout before starting moclobemide§	taper and stop clomipramine, then wait 21 days for washout before starting MAOI§
taper and stop moclobemide, then wait 24 hours for washout before starting above drug§	taper and stop moclobemide, then wait 24 hours for washout before starting reboxetine§	taper and stop moclobemide, then wait 24 hours for washout before starting above drug§	taper and stop moclobemide, then wait 24 hours for washout before starting clomipramine§		taper and stop moclobemide, then wait 24 hours for washout before starting MAOI§
taper and stop MAOI, then wait 14 days for washout before starting above drug§	taper and stop MAOI, then wait 14 days for washout before starting reboxetine§	taper and stop MAOI, then wait 14 days for washout before starting above drug§	taper and stop MAOI, then wait 21 days for washout before starting clomipramine§	taper and stop MAOI, start moclobemide while maintaining MAOI dietary restrictions for 14 days§	taper and stop MAOI, wait 14 days for washout before starting other MAOI§

* A washout period of 2–5 half-lives (most frequently 2–5 days) between cessation of previous drug and the introduction of a new drug is the safest switching strategy from the point of view of drug interactions. In the indicated instances a washout period is not essential if switching is carried out cautiously and under close observation, and clinical considerations such as illness severity support harm–benefit considerations. Cautious cross taper (when the dose of the first drug is being reduced and the dose of the second drug is being increased at the same time so that the patient is taking both antidepressants) may be used in the indicated instances if appropriate and safe.

† Fluoxetine may still cause interactions 5 or 6 weeks after cessation (especially from higher doses) due to long half-life of drug and active metabolite.

‡ Fluoxetine is likely to continue to elevate TCA concentrations for several weeks.

§ Co-prescription of the two antidepressants in this instance is not recommended.

Adapted from references 2, 8–10

DENTAL NOTE

Dental note

Oral and dental effects of antidepressants

Christopher Daly
Chair
Dental Therapeutics Committee
Australian Dental Association

Aust Prescr 2016;39:84
http://dx.doi.org/10.18773/austprescr.2016.035

Patients treated with antidepressant drugs may experience a dry mouth. Other drugs associated with dry mouth include antihistamines, anticholinergics, antihypertensives and antipsychotics. These drugs may cause salivary gland hypofunction, or may alter the threshold for the perception of dry mouth or they may do both.[1] Older patients appear to be more at risk of a drug-induced dry mouth, with greater salivary gland hypofunction, compared to younger adults.[2]

Among the antidepressant drugs, tricyclic antidepressants are associated with a higher incidence of dry mouth than selective serotonin reuptake inhibitors (SSRIs).[3] In a study of parotid gland salivary flow rates, patients taking tricyclic antidepressants had a 58% reduction in flow rates compared with untreated controls, while the flow rate was reduced by 32% with SSRIs.[3]

Patients with a dry mouth may complain of associated dryness of the lips and throat, oral soreness or burning, altered taste sensations and halitosis. They may find chewing, swallowing and speaking difficult. The risk of candidosis is increased.[4] The lack of an adequate salivary film between dentures and underlying gums can impair retention of dentures, and the lack of salivary lubrication can lead to denture-induced mucosal ulceration.

Saliva acts to buffer organic acids produced by dental plaque and maintains a remineralising environment within the oral cavity to preserve the teeth. A reduction in salivary flow rates is therefore thought to increase the risk of dental caries.[5] Patients with a dry mouth will often try to alleviate their symptoms by sucking sweet confectionery, chewing sugar-containing gums or by drinking cariogenic and acidic beverages. All of these can further increase the risk of tooth surface demineralisation and caries.

When patients are starting an antidepressant, it is important to inform them of the potential risk of developing a dry mouth and its possible adverse effects. Therapeutic Guidelines: Oral and Dental[6] recommends that before treatment patients should have a dental check-up followed by treatment of any active dental disease. Instruction in oral hygiene (and denture hygiene if dentures are used) should be given. Review appointments, to assess the oral and dental status, should be at 3–6 monthly intervals.

Therapeutic and preventive strategies are recommended to manage the oral and dental effects of dry mouth. Dental management involves the use of products that promote remineralisation of the teeth as a means of preventing caries. This may involve the use of topical fluoride applied in the dental surgery or the use of fluoride rinses or a high-strength fluoride toothpaste.[6] Use of a casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) cream is also recommended for remineralisation.[6] For both the high-strength fluoride toothpaste and the CPP-ACP cream, a 'spit don't rinse' strategy is recommended following application to the teeth.

In the management of dry mouth, oral lubricating gels or artificial saliva may be used for the transient relief of symptoms. Chewing of sugarless gum or CPP-ACP gum to stimulate saliva flow may be helpful. Therapeutic Guidelines: Oral and Dental[6] contains practical advice for patients with dry mouth and advises patients to avoid acidic beverages such as wine, fruit juices, soft drinks and sports drinks. They should limit their sugar intake and avoid sugary snacks in order to reduce the potential for demineralisation and caries. Use of a bicarbonate mouthwash is recommended on waking and at any time during the day for symptomatic relief.[6]

Conflict of interest: none declared

REFERENCES

1. Thomson WM. Dry mouth and older people. Aust Dent J 2015;60 Suppl 1:54-63. http://dx.doi.org/10.1111/adj.12284
2. Patel PS, Ghezzi EM, Ship JA. Xerostomic complaints induced by an anti-sialogogue in healthy young vs. older adults. Spec Care Dentist 2001;21:176-81. http://dx.doi.org/10.1111/j.1754-4505.2001.tb00251.x
3. Hunter KD, Wilson WS. The effects of antidepressant drugs on salivary flow and content of sodium and potassium ions in human parotid saliva. Arch Oral Biol 1995;40:983-9. http://dx.doi.org/10.1016/0003-9969(95)00079-5
4. McIntyre GT. Oral candidosis. Dent Update 2001;28:132-9.
5. Hopcraft MS, Tan C. Xerostomia: an update for clinicians. Aust Dent J 2010;55:238-44. http://dx.doi.org/10.1111/j.1834-7819.2010.01229.x
6. Oral and Dental Expert Group. Therapeutic Guidelines: oral and dental. Version 2. Melbourne: Therapeutic Guidelines Limited; 2012.

Secondary osteoporosis

SUMMARY

Secondary osteoporosis is less common than primary osteoporosis. It may be suspected in patients who present with a fragility fracture despite having no risk factors for osteoporosis. In addition, secondary osteoporosis should be considered if the bone density Z-score is –2.5 or less.

Consider the fracture site and presence of other clinical clues to guide investigations for an underlying cause. The tests to use are those that are indicated for the suspected cause.

Baseline investigations include tests for bone and mineral metabolism (calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone), liver and kidney function, full blood count and thyroid-stimulating hormone. More detailed testing may be required in patients with severe osteoporosis.

Angela Sheu
Advanced trainee[1]
Conjoint associate lecturer[2]

Terry Diamond
Senior endocrinologist[1]
Associate professor
Endocrinology[2]

[1] Department of Endocrinology
St George Hospital
[2] University of New South Wales
Sydney

Keywords
biopsy of bone, bone density, fracture of bone, osteoporosis, Z-score

Aust Prescr 2016;39:85–7
http://dx.doi.org/10.18773/austprescr.2016.038

Introduction

Secondary osteoporosis results from specific clinical disorders that are potentially reversible. Up to 30% of postmenopausal women and 50% of men with osteoporosis may have an underlying cause. The underlying pathogenesis of secondary osteoporosis is often multifactorial. Correctly treating the cause may ameliorate fracture risk and avoid unnecessary treatment with antiresorptive drugs.[1,2]

Clinical assessment

Secondary causes of osteoporosis should be considered in patients who suffer a fragility fracture when 'traditional' risk factors are insufficient to explain the injury. People with a bone mineral density Z-score –2.5 or less may also have secondary osteoporosis. (The Z-score is a comparison to age-matched, sex-matched individuals.)

Clues to an underlying secondary cause include an atypical fracture, the severity of osteoporosis and the presence of clinical features found through history and clinical examination (e.g. anaemia, malabsorption, amenorrhoea, constitutional symptoms or specific endocrinopathies) (see Table). A careful drug history may identify possible causes. While corticosteroids are well known to cause osteoporosis and fragility fractures, a number of other drugs also increase fracture risk (see Box). However, not all patients with secondary osteoporosis will present with the classic signs of the underlying condition. They may have subclinical disease at the time of their fracture or when the low bone mineral density is detected, with osteoporosis being the first manifestation of their underlying condition.

Identifying the cause

When a patient has clinical evidence of an underlying cause of osteoporosis, the necessary investigations may be straightforward. In an otherwise healthy patient with no specific clinical signs, a range of investigations may be required to identify a secondary cause of osteoporosis.

The prevalence of undiagnosed secondary causes of osteoporosis is unknown and there are no guidelines regarding appropriate laboratory tests for the otherwise healthy patient. In any patient suspected of having secondary osteoporosis, most experts recommend evaluation of bone and mineral metabolism with blood tests for calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone, liver and kidney function, full blood count and thyroid-stimulating hormone.

In those with severe osteoporosis (multiple fractures or bone mineral density T-score <–3.0) without specific clinical findings, additional tests should be performed. These tests include serum protein electrophoresis, free light chain assay, markers of inflammation, coeliac serology and total IgA, sex steroids (testosterone in men and oestradiol in women) and 24-hour urinary free cortisol.[3-7] A 24-hour urinary calcium collection is indicated if there are abnormalities of serum calcium or parathyroid hormone.

The role of bone turnover markers, such as telopeptides, in the diagnosis of osteoporosis is controversial. Currently, in specialists' clinics, their clinical role is in monitoring treatment efficacy.[8]

Several small cross-sectional studies have evaluated the yield of combined laboratory investigations in identifying an underlying cause of osteoporosis in otherwise asymptomatic patients. In studies of 173[9] and 204[4] postmenopausal women, the three most common findings were hypercalciuria, malabsorption (vitamin D deficiency) and hyperparathyroidism.

Table **Secondary causes of osteoporosis**

Disorder	Most common fracture site	Primary mechanism
Inflammatory conditions		
Rheumatoid arthritis, systemic lupus erythematosus	Hip	High bone turnover due to pro-inflammatory cytokines
Crohn's disease, ulcerative colitis	Vertebrae	High bone turnover due to pro-inflammatory cytokines, malnutrition and malabsorption
Hypogonadism		
Premature menopause (auto-immune, surgical, drugs)	Distal radius (Colles), vertebrae	High bone turnover from low oestrogen or low testosterone
Hypopituitarism (structural or functional)	Distal radius (Colles), vertebrae	High bone turnover from low oestrogen or low testosterone
Endocrinopathies		
Hypercortisolaemia (Cushing's syndrome)	Vertebrae, ribs	Low bone turnover from impaired bone formation and mineralisation
Hyperthyroidism	Hip	High bone turnover from increased bone resorption
Primary hyperparathyroidism	Distal radius, vertebrae	High bone turnover from increased bone resorption
Hyperprolactinaemia	Distal radius, vertebrae	High bone turnover from oestrogen deficiency
Acromegaly	Vertebrae	High bone turnover, increase in bone size and co-existing secondary hypogonadism
Diabetes mellitus	Hip	Low bone turnover from insulinopenia in type 1, mechanism not well understood in type 2
Malabsorption		
Pernicious anaemia	Vertebrae	Low bone turnover from impaired osteoblast recruitment
Coeliac disease	Distal radius, vertebrae	High bone turnover due to malnutrition and malabsorption
Gastrectomy	Vertebrae	High bone turnover due to malnutrition and malabsorption
Haematological conditions		
Multiple myeloma and monoclonal gammopathy of unknown significance	Vertebrae	Uncoupling in bone turnover (high bone resorption and low bone formation) from pro-inflammatory cytokines
Myeloproliferative disorders	Vertebrae	Direct marrow effects on bone
Systemic mastocytosis	Vertebrae	High bone turnover from mast cell mediators
Abnormal bone architecture		
Paget's disease	Long bones	High bone turnover from overactive bone resorption
Osteopetrosis	Hip, long bones	Low bone turnover due to defective bone resorption
Malignancy (primary or secondary)	Affected bones	High bone turnover from paraneoplastic effects
Other conditions		
Chronic liver disease	Vertebrae	Low bone turnover from liver disease and increased bone resorption due to malabsorption, vitamin D deficiency and hypogonadism
Chronic kidney disease	Hip, vertebrae	High bone turnover from osteomalacia, secondary hyperparathyroidism or mixed bone disease, or low bone turnover from adynamic bone disease (from aluminium or iron)
Kidney transplantation	Vertebrae, small bones	High bone turnover and tertiary hyperparathyroidism

In the study of 204 women, hyperparathyroidism was detected in 35%, although less than 10% had primary hyperparathyroidism with hypercalcaemia.[4] A cost–benefit analysis of the investigations was not performed in either of these studies.[4,9] There are no large studies assessing the frequency and cost–benefit of investigations for secondary osteoporosis.

Bone biopsy

In the past, bone histomorphometry was commonly used to assess the severity of osteoporosis before the advent of dual energy X-ray absorptiometry.

Bone biopsies are now rarely performed. In a highly select group of patients, bone biopsy performed and interpreted by an experienced specialist is useful in establishing the underlying aetiology and appropriate therapy of atypical cases if non-invasive methods have been inconclusive. Bone histomorphometry is a specialist tool to diagnose and assess:

- osteomalacia
- renal bone disease
- bone turnover (to differentiate between low- and high-turnover osteoporosis) with potential impact on therapeutic options.

In one specialist centre, 99 transiliac bone biopsies were performed over 14 years on 'atypical' cases of osteoporosis.[10] This represented 0.003% of patients reviewed for bone-related consultations.

Bone marrow and trephine biopsy is only required to exclude an underlying haematological cause for osteoporosis such as plasma cell dyscrasia, lymphoma or mastocyte disorders which will require specific therapies.

Box **Drugs that increase fracture risk**

Corticosteroids (≥5 mg prednisolone daily or equivalent for ≥3 months)
Antiepileptics: carbamazepine, phenytoin, phenobarbitone
Hypoglycaemics: thiazolidinediones, empagliflozin
Selective serotonin reuptake inhibitors
Excess thyroxine
Aromatase inhibitors
Tamoxifen (when used in pre-menopausal women)
Gonadotropin-releasing hormone
Chemotherapy
Immunosuppressants: cyclosporine, tacrolimus, methotrexate
Lithium
Heparin
Proton pump inhibitors
Aluminium-containing antacids
Depot medroxyprogesterone acetate
Antipsychotics

Conclusion

Secondary causes of osteoporosis are less common than primary osteoporosis, but correctly treating an underlying cause may be sufficient to ameliorate the increased fracture risk. Underlying causes should be suspected in patients with very low bone mineral density or in those without 'traditional' risk factors for fractures.

Confirming the diagnosis requires a careful history and physical examination for evidence of known causes and can be confirmed with selected laboratory investigations. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Primary hypoparathyroidism is present in approximately a third of patients with secondary osteoporosis
2. Hyperparathyroidism may be a cause of secondary osteoporosis

Answers on page 107

REFERENCES

1. Fitzpatrick LA. Secondary causes of osteoporosis. Mayo Clin Proc 2002;77:453-68. http://dx.doi.org/10.1016/S0025-6196(11)62214-3
2. Polymeris A, Michalakis K, Sarantopoulou V. Secondary osteoporosis - an endocrinological approach focusing on underlying mechanisms. Endocr Regul 2013;47:137-48. http://dx.doi.org/10.4149/endo_2013_03_137
3. Adler RA. Laboratory testing for secondary osteoporosis evaluation. Clin Biochem 2012;45:894-900. http://dx.doi.org/10.1016/j.clinbiochem.2012.01.024
4. Cerdá Gabaroi D, Peris P, Monegal A, Albaladejo C, Martínez MA, Muxí A, et al. Search for hidden secondary causes in postmenopausal women with osteoporosis. Menopause 2010;17:135-9. http://dx.doi.org/10.1097/gme.0b013e3181ade8e5
5. Ferrari S, Bianchi ML, Eisman JA, Foldes AJ, Adami S, Wahl DA, et al.; IOF Committee of Scientific Advisors Working Group on Osteoporosis Pathophysiology. Osteoporosis in young adults: pathophysiology, diagnosis, and management. Osteoporos Int 2012;23:2735-48. http://dx.doi.org/10.1007/s00198-012-2030-x
6. Hofbauer LC, Hamann C, Ebeling PR. Approach to the patient with secondary osteoporosis. Eur J Endocrinol 2010;162:1009-20. http://dx.doi.org/10.1530/EJE-10-0015
7. The Royal Australian College of General Practitioners. Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men. Melbourne: RACGP; 2010. http://www.racgp.org.au/your-practice/guidelines/musculoskeletal/osteoporosis [cited 2016 May 1]
8. Lee J, Vasikaran S. Current recommendations for laboratory testing and use of bone turnover markers in management of osteoporosis. Ann Lab Med 2012;32:105-12. http://dx.doi.org/10.3343/alm.2012.32.2.105
9. Tannenbaum C, Clark J, Schwartzman K, Wallenstein S, Lapinski R, Meier D, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J Clin Endocrinol Metab 2002;87:4431-7. http://dx.doi.org/10.1210/jc.2002-020275
10. Kann PH, Pfützner A, Delling G, Schulz G, Meyer S. Transiliac bone biopsy in osteoporosis: frequency, indications, consequences and complications. An evaluation of 99 consecutive cases over a period of 14 years. Clin Rheumatol 2006;25:30-4. http://dx.doi.org/10.1007/s10067-005-1132-7

ARTICLE

Where to find information about drugs

Richard O Day
Clinical Pharmacology and Toxicology
St Vincent's Hospital
UNSW Medicine

Leone Snowden
NSW Medicines Information Centre
Sydney

Keywords
complementary medicines, drug information, drug interaction

Aust Prescr 2016;39:88–95
http://dx.doi.org/10.18773/austprescr.2016.023

SUMMARY

Good medicines information is critical to medical practice. Choose high-quality, pre-appraised sources first and make sure they are current.

Select the information that is most relevant to the needs of your particular patient.

Take the time to become familiar with the features of the resources you use. Australian Medicines Handbook, Therapeutic Guidelines, *Australian Prescriber* and NPS MedicineWise cover most routine clinical practice needs.

Introduction

Using reliable information resources informs safe and consistent practice. There is so much information available on medicines that it can be hard to identify accurate, current, unbiased and evidence-based resources.

Questions to consider when selecting an information source

Not all information sources are reliable, so it is useful to ask yourself some simple questions to help you appraise them.

Is it evidence-based?

Save time by looking at high-quality, pre-appraised evidence sources first, such as the Australian Medicines Handbook (AMH), Therapeutic Guidelines and BMJ Best Practice. These are sources which have done the work of searching and critically appraising the evidence for you. They integrate this evidence with expert review to produce the best advice currently available. Systematic reviews and meta-analyses are the next best evidence. Reviews that are not systematic, older texts, and clinical trial reports (even randomised controlled trials) are lower quality evidence and require critical appraisal.

Is it current?

Check the date of publication or review date for guidelines, websites and texts. Older information and texts should be used with caution. Medicine changes rapidly and many previously accepted practices have later been shown to be incorrect.

Is it relevant to your patient?

The type of information you require dictates where you should look first. Consider individual patient needs. Specific information may be needed for older people, children, pregnant or lactating women, those with organ impairment or comorbidities (see Table).

Sources of medicines information

AMH, Therapeutic Guidelines and NPS MedicineWise cover most commonly prescribed medicines and conditions and should be among the first resources consulted. This information is evidence-based, current and reflects Australian best practice. The layout of AMH and Therapeutic Guidelines also allows rapid access to the information needed to prescribe safely.

NPS MedicineWise and *Australian Prescriber* provide free, reliable, independent information on drugs and therapeutics. NPS MedicineWise produces a number of resources prescribers can rely on to stay informed. *Australian Prescriber* covers therapeutic issues and controversies, new drugs and their place in therapy, and provides practical reviews on drug use and diagnostic tests.

Resources like BMJ Best Practice, Clinical Evidence, DynaMed Plus, UpToDate, and current evidence-based guidelines provide rapid access to information on treatment of specific conditions and should be consulted next.

An alphabetical listing of resources and access methods to drug information is given in the Box.

Pharmaceutical companies can provide information on their own products, including detailed information on stability, excipients and adverse effects.

Product information and consumer medicines information

The product information contains basic information on a medicine including its ingredients, pharmacokinetics, mechanism of action, approved indications, doses, contraindications, precautions, adverse effects and appearance. It does not contain comparative information. The product information is written by the pharmaceutical company sponsor, then reviewed and amended by the Therapeutic Goods Administration (TGA).

Table **Sources of drug information – a quick guide**

Category	Recommended sources	Electronic format	Comments
General			
Brief, evidence-based, current	AMH	M	Print and online
Product information	TGA*		TGA website lists most current product information
	MIMS	i,A,M	Has unique additional features
	AusDI	M	Has unique additional features
New drugs	NPS Radar*		
	*Australian Prescriber**	M	
	AusPAR*		From TGA website – detailed information on safety, efficacy, pharmacokinetics and actions
	PBS public summary documents*		From PBS website – information on decisions to subsidise or not subsidise
Detailed	Micromedex	i,A	Print and online, may be available free to public hospital employees, students, universities
	Martindale – the Extra Pharmacopoeia		Martindale also available via Micromedex, BMJ Best Practice
	AHFS Drug Information		Print and online, published yearly
	AusPAR*		Particularly for new drugs or newly approved indications
Pharmacology	Goodman and Gilman's The Pharmacological Basis of Therapeutics	ebook	Classic pharmacology text
Pharmacokinetics	Goodman and Gilman's The Pharmacological Basis of Therapeutics, Micromedex, product information*		
	Pharmacokinetics Made Easy		Information on pharmacokinetic principles, not individual drugs
Therapeutic choice			
Brief, evidence-based, current	Therapeutic Guidelines	M	Print (individual subject titles) and online (eTG Complete)
Information on new drugs, therapeutics, evolving issues	NPS MedicineWise – Heath News & Evidence*, MedicineWise News*, RADAR*		Australian
	Australian Prescriber – The Doctor's Bag app*	i,A	App covers doses of emergency drugs in the PBS Prescriber Bag, and anaphylaxis management
	AusPAR*		
Detailed	BMJ Best Practice, DynaMed, Clinical Evidence	i,A,M	
Guidelines	NHMRC guidelines portal*		Australian
	RACGP clinical guidelines, endorsed resources and accepted clinical resources*		
	NICE* (UK), SIGN* (UK), National Guideline Clearinghouse* (USA)		Non-Australian sources may recommend treatments not available locally
Rarer conditions	UpToDate	i,A,M	Subscription rates vary

* information is free, A android app available, i iPhone app available, M mobile website

Table **Sources of drug information – a quick guide (continued)**

Category	Recommended sources	Electronic format	Comments
Drug interactions			
Basic information	Product information (available through TGA*, NPS MedicineWise*, MIMS, AusDI), AMH		Further detail may need to be sought
Alerts	Available in most prescribing and dispensing software		Generally brief information, further detail may need to be sought
Interaction checkers	Micromedex, Lexi-Interact	i,A	Lexi-Interact available via UpToDate (extra fee)
	MIMS, AusDI		
	Natural Medicines database		Covers complementary and alternative medicines + traditional medicine interactions
Detailed information	Stockley's Drug Interactions		Print and online, authoritative texts
Complementary and alternative medicine interactions	Natural Medicines database		Online
	Stockley's Herbal Medicines Interactions		Print and online via Medicines Complete
Free interaction checkers	Medscape*		Has other useful features
	Epocrates*	i,A	Has other useful features and additional paid content
Other sources			
Drugs in pregnancy and lactation	The Women's Pregnancy and Breastfeeding Medicines Guide		Australian, brief and clear information, now available as an online database (see page 105)
	Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk		Print and online, excellent text
	Micromedex (Reprorisk database)		
	MotherSafe*, Royal Women's Hospital Obstetric Drug Information Service*		Specialist phone services
	LactMed*		Practical, detailed information (US National Library of Medicine)
	Medications and Mothers Milk	i,A	Print and online
Drugs in paediatrics	AMH Children's Dosing Companion	M	
	PEMSoft	i,A	
	NeoFax	i	Information on drug use in neonates, available as an extra subscription from Micromedex
	Paediatric Injectable Guidelines, Pediatric Injectable Drugs (The Teddy Bear Book)		Specialist texts on administration of parenteral medicines to children
	Paediatric Emergency Medication Book		Medication dosing for resuscitation (see page 95)
Complementary and alternative medicines	Natural Medicines database		Online. Provides detailed information on complementary and alternative medicines, and a drug interaction checker
	Stockley's Herbal Drug Interactions		Print and online
	Medicines Complete (online versions of Stockley's Herbal Drug Interactions, Herbal Drugs, and Dietary Supplements)		Online
	MedlinePlus*		
	National Centre for Complementary and Integrative Health*		

Table **Sources of drug information – a quick guide (continued)**

Category	Recommended sources	Electronic format	Comments
Other sources (continued)			
Administration of medicines	Product information*, MIMS, AusDI		Brief information
	Martindale, AHFS Drug Information		More detailed information
	Micromedex IV Compatibility	i	
	Australian Injectable Drugs Handbook		Information on administration routes, rates, and compatibility of injectable medications
	Australian Don't Rush to Crush Handbook	M	Print and online via MIMS, information on crushing and dissolving drugs for patients with swallowing difficulty or receiving enteral tube feeds
	Handbook of Drug Administration via Enteral Feeding Tubes		UK text
Renal impairment	Product information*, AMH, Therapeutic Guidelines		Brief information
	Micromedex, Martindale, AHFS Drug Information		Detailed information
	The Renal Drug Handbook		Print and online, detailed UK resource
	Seyffart's Directory of Drug Dosage in Kidney Disease		Detailed European resource, lacks information on continuous renal replacement therapies
Databases	PubMed*/Medline, Embase		References from these sources require critical appraisal
Evidence-based medicine resources	Evidence Search (NICE, UK)*		
	Cochrane library*		
	TRIP database*		Results filtered on relevance, quality and currency
Consumer information			
Official CMI	Available through TGA*, MIMS, AusDI, NPS MedicineWise		Official basic industry-written, TGA-approved information
Other information*	NPS MedicineWise		
	HealthDirect		
	Better Health Channel		Funded by the Victorian Government
	UpToDate patient information		Information often US based
	MedlinePlus (USA)		
	Mayo Clinic (USA)		

* information is free
A android app available
i iPhone app available
M mobile website
AMH Australian Medicines Handbook
AusDI Australian Drug Information
AusPAR Australian Public Assessment Report
CMI Consumer Medicines Information
IV intravenous
MIMS originally Monthly Index of Medical Specialties
NHMRC National Health and Medical Research Council
NICE National Institute for Health and Care Excellence (UK)
PBS Pharmaceutical Benefits Scheme
RACGP Royal Australian College of General Practitioners
SIGN Scottish Intercollegiate Guidelines Network (UK)
TGA Therapeutic Goods Administration
TRIP Turning Research into Practice

Box Alphabetical list of resources and access methods to drug information

AHFS Drug Information 2016. American Society of Health-System Pharmacists. www.ahfsdruginformation.com

AusDI www.ausdi.com.au

AusPARs www.tga.gov.au/auspars-questions-answers

Australian Don't Rush to Crush Handbook: Therapeutic Options for People Unable to Swallow Solid Oral Medicines. Society of Hospital Pharmacists of Australia. www.shpa.org.au

Australian Injectable Drugs Handbook. Society of Hospital Pharmacists of Australia. www.shpa.org.au

Australian Medicines Handbook http://shop.amh.net.au

Australian Prescriber www.nps.org.au/australianprescriber

Better Health Channel www.betterhealth.vic.gov.au

BMJ Best Practice http://bestpractice.bmj.com/best-practice/welcome.html

Cochrane Library www.cochrane.org

Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 10th ed. Briggs GG, Freeman RK. Philadelphia (PA): Lippincott Williams & Wilkins; 2015.

DynaMed Plus www.dynamed.com/home

Epocrates www.epocrates.com

Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. Brunton LL, editor. New York: McGraw-Hill; 2011.

LactMed http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Lexi-Interact http://webstore.lexi.com/Lexi-Interact (also available via UpToDate and Lexicomp subscriptions)

Martindale: The Complete Drug Reference. 38th ed. Brayfield A, editor. London: Pharmaceutical Press; 2014.

Mayo Clinic (USA) www.mayoclinic.org

MedlinePlus (USA) www.nlm.nih.gov/medlineplus

MedlinePlus Herbs and Supplements www.nlm.nih.gov/medlineplus/druginfo/herb_All.html

Medscape www.medscape.com

Micromedex Solutions [Database] www.micromedexsolutions.com

MIMS Australia www.mims.com.au

National Centre for Complementary and Integrative Health https://nccih.nih.gov and https://nccih.nih.gov/health/providers

National Guideline Clearinghouse (USA) www.guideline.gov

Natural Medicines https://naturaldatabase.therapeuticresearch.com/Logon.aspx?cs=&s=ND

NeoFax [Database] http://micromedex.com/neofax-pediatric

NHMRC Guidelines www.nhmrc.gov.au/guidelines-publications

NHS Evidence (UK) www.evidence.nhs.uk

NICE (UK) www.nice.org.uk

NPS MedicineWise www.nps.org.au

NPS Radar www.nps.org.au/radar

Paediatric Emergency Medication Book. Craig S, editor. Melbourne: Monash Children's Hospital; 2014.

Paediatric Injectable Guidelines. Royal Children's Hospital Melbourne. http://pig.hcn.com.au

PBS Public Summary Documents www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd

Pediatric Injectable Drugs (The Teddy Bear Book). 10th ed. Phelps SJ, Hagemann TM, Lee KR, Thompson AJ. Bethesda (MD): American Society of Health-System Pharmacists; 2013.

PEMSoft https://health.ebsco.com/products/pemsoft

Pharmacokinetics Made Easy. 2nd ed. Birkett DJ. Sydney: McGraw-Hill Education; 2009.

Pregnancy and Breastfeeding Medicines Guide. The Royal Women's Hospital. https://thewomenspbmg.org.au

RACGP Clinical Guidelines www.racgp.org.au/your-practice/guidelines

RACGP Endorsed Resources and Accepted Clinical Resources www.racgp.org.au/support/advocacy/repsandendorsements/endorsements/#endorsements

Seyffart's Directory of Drug Dosage in Kidney Disease. Seyffart G. Munich: Dustri-Verlag; 2011.

Stockley's Drug Interactions www.medicinescomplete.com/mc/index.htm

Stockley's Drug Interactions. 11th ed. Preston CL, editor. London: Pharmaceutical Press; 2016.

Stockley's Herbal Medicines Interactions www.medicinescomplete.com/mc/index.htm

Stockley's Herbal Medicines Interactions. 2nd ed. Williamson E, Driver S, Baxter K, editors. London: Pharmaceutical Press; 2013.

TGA www.tga.gov.au

TGA Prescribing Medicines in Pregnancy Database www.tga.gov.au/prescribing-medicines-pregnancy-database

The Doctor's Bag app (*Australian Prescriber*) www.australianprescriber.com/the-doctors-bag

Therapeutic Guidelines www.tg.org.au

TRIP Database www.tripdatabase.com

UpToDate www.uptodate.com/home

UpToDate Patient Information www.uptodate.com/contents/table-of-contents/patient-information

For older or off-patent drugs, the product information may not reflect current accepted practice, and adverse effects and interactions information may not be up to date. For example, metformin is widely and safely used for type 2 diabetes in patients with creatinine clearances less than 60 mL/minute, despite this practice being contraindicated in the product information. Polycystic ovary syndrome is a recognised indication for metformin but is not listed in the product information.

The consumer medicines information is also written by the pharmaceutical company. It is based on the product information and provides clear, unbiased information to help patients take medicines safely.

The current product information and consumer medicines information are available from the TGA website, NPS MedicineWise and from compendia like MIMS and AusDI (previously AusDI Advanced or Catalyst). Many prescribing software packages use MIMS as their information source, while AusDI is the information source behind Medical Director.

Both MIMS and AusDI write their own abbreviated information for drugs and have features such as interaction checkers, gluten content, use in sport, and searchable product images that can help identify tablets and capsules. Each also has unique features. For an additional cost MIMS includes information on crushing or dissolving products for patients with swallowing difficulties or nasogastric tubes from the Society of Hospital Pharmacists of Australia's (SHPA) publication the Australian Don't Rush to Crush Handbook.

AusDI's unique features include information on lactose and latex content, and detailed independent drug monographs which cover approved and unapproved uses, mechanism of action, pharmacokinetics, interactions, dosage in age groups and organ failure, and use in pregnancy and lactation.

Australian Public Assessment Report

Australian Public Assessment Reports (AusPARs) are summaries of the TGA's evaluation of a new drug or changes to indications of an existing drug. It includes reasons for accepting or rejecting applications and detailed information on the quality, safety and efficacy of a drug. AusPARs are a useful source of information on new drugs not yet covered by pre-appraised references.

Public summary documents

Pharmaceutical Benefits Scheme (PBS) public summary documents outline the rationale behind the recommendations made by the Pharmaceutical Benefits Advisory Committee on whether or not a drug should be subsidised. They include information on the drug's place in therapy, the evidence considered, financial impact, and the reasons for decisions.

Pharmacology texts and databases

Pharmacology texts provide information on how drugs work, how they compare to other drugs, their pharmacokinetics, interactions and uses. Goodman and Gilman's The Pharmacological Basis of Therapeutics is considered the gold standard text on pharmacology but there are many others. Pharmacokinetics Made Easy is a simple and helpful guide to practical pharmacokinetics.

Micromedex is a database containing drug monographs, an interaction checker, information on intravenous compatibility, drug use in pregnancy, Martindale (the UK standard reference on drugs), and a toxicology database (Poisindex). Some features require additional subscriptions. The monographs have detailed information on clinical use, adverse effects and comparative efficacy.

Clinical decision support tools

Clinical decision support tools help with diagnosis and treatment decisions at the point of care. They provide access to evidence-based guidelines and treatment algorithms. Some examples are BMJ Best Practice (based on BMJ's Clinical Evidence), DynaMed, and PEMSoft (Paediatric Emergency Management).

Other evidence-based medicine sources

The TRIP database (Turning Research into Practice) is a search engine designed to find high-quality evidence quickly. Results can be filtered by type, for example systematic reviews, and scored for relevance, quality (by publisher) and currency, with higher ranked results appearing first.

The National Institute for Health and Care Excellence (NICE) provides Evidence Search, a search engine of several authoritative UK sources. The Cochrane Library is free within Australia and provides access to Cochrane reviews, critiques of other systematic reviews, economic evaluations and a large database of controlled trials.

Evidence-based guidelines such as Therapeutic Guidelines and the RACGP clinical guidelines provide information on diagnosis and treatment in specific conditions, but usually have little information on drugs other than dosage and indications.

UpToDate provides information on diagnosis and pathophysiology, but therapeutic recommendations may not be consistent with Australian practice. It may be useful for information on rarer conditions, for example those not covered by Therapeutic Guidelines.

Bibliographic databases

PubMed/Medline and Embase provide access to the medical literature and should ideally be used together. Both cover the major medical journals but they also have unique content, so using only one may mean that essential references are missed. Learning how to use them well can save time and improve the quality of information retrieved. The 'Clinical Queries' filters can save time by restricting results to clinical studies. If you do not have the time or skills to search properly, consult a medical librarian or medicines information specialist. Information found from literature searches requires critical appraisal.

Drug interactions

Many prescribing and dispensing software packages automatically check for drug interactions. MIMS, AusDI, Micromedex, Lexicomp, and UpToDate all provide interaction checkers. More detailed information on interactions and their management is available from specialised texts and databases such as Stockley's Drug Interactions.

Drug use in pregnancy and lactation

The product information rarely contains useful information on drug use in pregnancy or lactation.[1] The Women's Pregnancy and Breastfeeding Medicines Guide provides brief information on the safety of drug use in pregnancy by trimester, and in lactation. The print version was replaced by an online database in July 2015. More detailed information can be found in Briggs and Freeman's Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.

Micromedex has information on drug risk in pregnancy via the three databases in Reprorisk. There are two telephone advisory services: MotherSafe (NSW) and the Royal Women's Hospital (Victoria). Lactation resources include Medications and Mothers Milk (print and online), and free fact sheets from LactMed.

Paediatric drug dosing

The product information and standard texts often provide minimal advice on dosing in children. The AMH Children's Dosing Companion (which has replaced the Royal Children's Hospital's Paediatric Pharmacopoeia) contains information on drugs commonly used in children, but lacks information for premature neonates.

Complementary and alternative medicines

Reliable information on complementary and alternative medicines (including herbs and products used with or instead of conventional medicines) is harder to find than for conventional medicines.

One of the best resources is the Natural Medicines database. It has an interaction checker which includes conventional medicines and complementary and alternative medicines. The database also has information on indications, safety, efficacy, adverse effects, nutrient depletions, and use of complementary and alternative medicines in pregnancy, lactation and sport.

Medicines Complete offers three online resources – Herbal Medicines, Dietary Supplements and Stockley's Herbal Medicines Interactions. Reliable free information is available from MedlinePlus Herbs and Supplements and the National Centre for Complementary and Integrative Health, a US National Institutes of Health resource.

Drug administration

Information on drug administration beyond what is available in the product information is found in two Society of Hospital Pharmacists of Australia publications:

- the Australian Don't Rush to Crush Handbook (print, or online as an add-on subscription in MIMS) provides advice on which medicines can be altered for patients with difficulty swallowing or receiving tube feeds
- the Australian Injectable Drugs Handbook outlines the preparation, compatibility, administration, and stability of injectable drugs.

Renal impairment

The product information, AMH and Therapeutic Guidelines provide some advice on dosing in renal impairment with Martindale, AHFS Drug Information and Micromedex providing more detail. The Renal Drug Handbook contains more detail still. The Renal Drug Reference Guide, an Australian text, is also excellent but has not been updated since 2007.

Keeping up to date

The volume of new information published means keeping up to date is a challenge. NPS Radar, *Australian Prescriber's* new drugs section, NICE's Medicines Awareness Daily and Medscape can help by summarising important new information. Subscribing to the table of contents of relevant journals is also useful to keep up to date with new developments.

Where not to look

Wikipedia, Google and internet searches can uncover worthwhile information but they should not be relied on as the primary source of drug information. They provide background information

and show what information patients may be reading. While Google Scholar may retrieve more scholarly publications, searching is less precise than with medical databases and the quality of results is not consistent. It can be worth checking Google Scholar for full text articles. Finding the few useful references in Google or Google Scholar often takes far longer than a medical database search. PubMed/Medline, Embase, Cochrane and the TRIP database will provide more reliable references, and more precise results.

Conclusion

Your patients will benefit from the time you take to learn what resources best answer specific questions about medicines and their use. Seek advice if you are unable to find the information you need. NPS MedicineWise maintains a list of medicines resources including telephone services and free Australian resources. ⋖

Conflict of interest: none declared

REFERENCE

1. Kennedy D. Classifying drugs in pregnancy. Aust Prescr 2014;37:38-40. http://dx.doi.org/10.18773/austprescr.2014.018

Book review

Paediatric Emergency Medication Book

Monash Children's Hospital Resuscitation Committee
Edited by Simon Craig
Melbourne: Monash Children's Hospital; 2014.
86 pages

This book provides a quick, easy-to-access, weight-based guide to resuscitation of infants and children. It includes medication dosing in resuscitation situations, endotracheal tube size and positioning, and emergency management of seizures, asthma, anaphylaxis and electrolyte disorders. The formatting, content and presentation have been carefully considered to achieve this aim and to make it a valuable resource.

Weight-based guidelines are presented for 2–80 kg, in a clear colour-coded format. The information for each weight is presented over two pages. It provides everything you need in a resuscitation setting at a glance, including tables for resuscitation, endotracheal tube size, and induction and paralytic drugs.

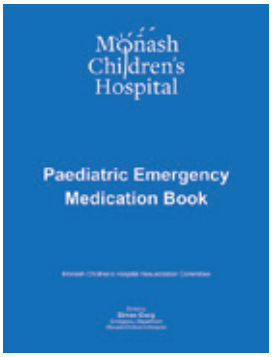
Information on drugs used in severe asthma, status epilepticus and electrolyte abnormalities is also included. Layout is the same irrespective of the weight selected which helps readers to become familiar with this resource. Infusion guidelines are also provided, although many institutions may have these preprogrammed in their infusion pumps.

The book is spiral bound with sturdy laminated pages, making it waterproof and durable. It is easy to turn to the weight needed and access the information required in a timely fashion. The first three pages contain Advanced Paediatric Life Support (APLS) algorithms for basic and advanced life support, and status epilepticus.

This is an excellent resource for medical and nursing staff working with sick infants and children, be that frequently or occasionally, in an inpatient ward setting, mixed emergency department or paediatric emergency department. It provides clear, easily accessible important information in a visually appealing format. The section on electrolyte abnormalities is particularly useful. It could also be used as a resource for education and specifically simulation – APLS Australia have already adopted it for this use.

Fiona Thomson
Paediatric emergency physician
Lady Cilento Children's Hospital
Senior lecturer
University of Queensland
Brisbane

Aust Prescr 2016;39:95
http://dx.doi.org/10.18773/austprescr.2016.036



ARTICLE

Dealing with drug-seeking behaviour

Jenny James
Medical coordinator
Substance Misuse Program
Sydney West Aboriginal Health Service
Sydney

Keywords
benzodiazepine, drug abuse, drug-seeking behaviour, general practice, opioid

Aust Prescr 2016;39:96–100
http://dx.doi.org/10.18773/austprescr.2016.022

SUMMARY

People who misuse prescription drugs most commonly seek prescriptions for opioids and benzodiazepines. Other prescription drugs that are misused include the newer antipsychotics such as quetiapine and olanzapine, and stimulants such as dexamphetamine and methylphenidate.

Health professionals should be aware of behaviours that may indicate drug seeking, but dependency on prescription drugs can occur at any age, within any cultural group and across any educational class. Patients with dependencies may not necessarily display obvious drug-seeking behaviours.

All general practices should have a practice policy on prescribing drugs of dependence. GPs should register with the Prescription Shopping Information Service.

There is strong evidence in Australia of increasing harms from prescription drugs of dependence, including deaths from overdose. Before prescribing any drug of dependence, health professionals require an understanding of the patient's biopsychosocial status, and the evidence-based indications and potential significant harms of these drugs.

Introduction

Increasing harms from prescription drugs of dependence are evident in Australia. Between 2001 and 2012 over 800 Australians died from overdoses that involved the prescription analgesic oxycodone, either alone or in combination with other drugs.[1] People may seek prescriptions for drugs of dependence with the intention of misuse.

Drug misuse occurs when patients consume either prescribed or illicit substances in a manner that is not consistent with legal or medical guidelines. Patients may be seeking drugs for themselves or to pass on to a family member with dependency issues. They may also seek to procure these drugs for diversion and monetary gain.

Drug-seeking behaviour is a commonly used, although poorly defined, term that describes a range of activities directed towards attainment of sought-after drugs. It requires an approach that is mindful of outcomes for the patient, practice staff and the community. General practitioners and pharmacists can be part of the solution to dangerous misuse of prescription drugs.

Which drugs do people seek?

Benzodiazepines and opioids are the two most common classes associated with drug-seeking behaviour. Opioids commonly misused in Australia include oxycodone, fentanyl, codeine and morphine.

Psychotropic drugs producing stimulant effects, euphoria, sedation or hallucinatory effects are sometimes sought. These include the newer antipsychotics quetiapine and olanzapine, and stimulants such as dexamphetamine and methylphenidate.[2] Anabolic steroids are also increasingly misused.

Misuse of medicines

The National Drug Strategy Household Survey 2013 found that misuse of prescribed drugs of dependence has increased for many years, while the proportion of people using most illegal drugs has remained relatively stable.[3] Opioid misuse in Australia now mainly involves opioids obtained on prescription.[4] Oxycodone was the seventh leading drug prescribed in general practice in 2014.[2] Data from needle and syringe programs in Australia show that in 7% of injecting episodes 'the last drug injected' by their clientele in 2000 was a prescription opioid. This rose to 27% in 2010.[2] There have been large increases in opioid prescribing,[5] with the total number of prescriptions on the Pharmaceutical Benefits Scheme (PBS) increasing about threefold between 1992 and 2007 (2.4 million to 7 million scripts).[4]

Over-the-counter combinations of codeine with paracetamol or ibuprofen have caused serious harms when misused.[6] Complications of overdose with the ibuprofen/codeine combinations can be life threatening and include gastrointestinal bleeding, perforation, hypokalaemia, renal failure, anaemia and opioid dependence.

In the last 10 years, benzodiazepine prescribing has increased, but there has also been a dramatic change in the profile of the benzodiazepines prescribed. Over a five-year period the prescription of alprazolam increased by a third, particularly on private (non-PBS) prescriptions.[7] The PBS-subsidised use of alprazolam, for the treatment of panic disorder, changed from Schedule 4 to Schedule 8 in February 2015 and it is expected that this will result in a decline of prescriptions for alprazolam. However all benzodiazepines can be misused.

Harms of misuse

Many coroners' inquests have drawn attention to deaths due to prescription opioids and psychotropic drugs. Most Australian deaths involving oxycodone were caused by combined drug toxicity. The most commonly co-administered drugs included benzodiazepines, alcohol and other opioids which in combination can cause respiratory depression. Approximately 12% of deaths were identified as due to oxycodone toxicity alone.[1]

Patterns of drug-seeking behaviour, intoxication and withdrawal states can affect patients' relationships, employment and finances. Misuse of prescription drugs is associated with crime and consequent incarceration. Harms extend to the wider community and include robbery, theft, identity fraud, extortion and the manufacture of illicit drugs. Traffic accidents and disorganised behaviour can have consequences for both the patient and community. Harms associated with the injection of prescription drugs include an increased risk of acquiring blood-borne viruses and other adverse effects of unsafe injecting.

Recognition of drug-seeking behaviour

Dependency on prescription drugs may occur at any age, within any cultural group and across any educational class. GPs should be aware of drug-seeking behaviours (Box 1),[8] but some patients seeking drugs of dependence may present without these behaviours. Common contexts within which drug-seeking occurs include:

- the development of dependence arising out of the use of prescription and over-the-counter opioids, benzodiazepines and other psychotropic drugs
- the use of prescription opioids by individuals dependent on illegal opioids such as heroin, partly as a result of substantial unmet demand for treatment of illicit opioid dependence. This includes patients who may wish to inject or sell these drugs
- drug diversion by people who want to sell the drugs
- the use of prescription drugs of dependence by patients who would never self-identify with 'people who use drugs.' These patients may self-medicate to feel better, and may present without immediately obvious signs of drug-seeking behaviour. Patients may appear to be socially advantaged with high achievements in education, adequate social supports and good incomes.

Box 1 Indicators of drug-seeking behaviours

Typical requests and complaints

Aggressively complaining about a need for a drug
Asking for specific drugs by name
Asking for brand names
Requesting to have the dose increased
Claiming multiple allergies to alternative drugs
Anger or irritability when questioned closely about symptoms such as pain

Inappropriate self-medicating

Taking a few extra, unauthorised doses on occasion
Hoarding drugs
Using a controlled substance for non-pain relief purposes (e.g. to enhance mood, aid sleep)
Injecting an oral formulation

Inappropriate use of general practice

Visiting multiple doctors for controlled substances (doctor shopping)
Frequently calling the clinic
Frequent unscheduled clinic visits for early refills
Consistently disruptive behaviour when arriving at the clinic
Consistently calling outside of clinic hours or when a particular doctor who prescribes controlled substances is on call

Resistant behaviour

Unwilling to consider other drugs or non-drug treatments
Frequent unauthorised dose escalations after being told that it is inappropriate
Unwilling to sign controlled substances agreement
Refusing diagnostic workup or consultation

Manipulative or illegal behaviour

Claiming to be on a waiting list for, or unable to afford, dental work and needing to manage dental pain
Obtaining controlled drugs from family members (including stealing from older relatives)
Using aliases
Forging prescriptions
Pattern of lost or stolen prescriptions
Selling drugs
Obtaining controlled drugs from illicit sources

Other typical behaviours

Being more concerned about the drug than a medical problem
Deterioration at home or work or reduction of social activities because of adverse drug effects

Adapted with permission from The Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part A – Clinical governance framework. Melbourne: RACGP, 2015.[8]

GPs can seek help from the Medicare Prescription Shopping Information Service by ringing to find out if a patient has been identified as a prescription shopper in the previous three months (Box 2). If the patient meets the program's criteria, the GP is informed straight away and can request further detail on the amount and type of PBS medicine supplied to the patient. The patient's consent is not necessary for the inquiry.

There are two caveats about the reports provided by the Prescription Shopping Information Service. Some patients who have met the criteria over a three-month period may not necessarily be prescription shopping. Target drugs include analgesics, antiepileptics, antiparkinson drugs, psychotropics and antidepressants, all of which the patient may need. Conversely, some patients with prescription drug dependency will not be identified by the Prescription Shopping Information Service because the 'bar' is set quite high. Additionally, non-PBS private prescriptions are not captured in the Prescription Shopping Information Service data.

If a patient does not meet the Prescription Shopping Information Service criteria, GPs can ask the patient to agree to the release of Medicare and PBS claims information. However, there is a time delay of several weeks before this information is sent and it always requires the patient to sign a release-of-information form (Box 2).

Box 2 **Prescription Shopping Information Service and release of information**

Prescription Shopping Information Service

Phone 1800 631 181: requires initial registration by GP

No patient consent required

Information available immediately

Further information and registration process available at: www.medicareaustralia.gov.au/provider/pbs/prescription-shopping/faq.jsp

Covers last 3 months

Criteria: must have been prescribed items by 6 or more prescribers and/or 25 or more target items, and/or 50 or more items

No information about private prescriptions

Medicare and PBS release of information

Form available at: www.humanservices.gov.au/spw/customer/forms/resources/2690-1003en.pdf

Patient consent required

Information only available after several weeks

Covers last 3 months

Criteria: all Medicare claimable doctor visits and all items dispensed on PBS

No information about private prescriptions

PBS Pharmaceutical Benefits Scheme

How to deal with requests for prescription drugs of dependence

In general practice, managing requests for prescription drugs of dependence requires a team approach involving the whole practice.

Practice policy

All practices need a policy on prescribing drugs of dependence. Team work and consistency of prescribing are essential. Community pharmacists can be made aware of the practice policy and also invited to be part of care planning for patients receiving drugs of dependence.[9] The practice policy should be comprehensive (Box 3) and understood and applied by all staff.[8] It should be explained to patients requesting drugs of dependency from the outset. This will diminish the chance of harms befalling the patient and of patients continuing to display challenging behaviours.

The practice policy also needs to be communicated to specialists, particularly neurologists and psychiatrists, who are external to the practice in order to avoid patients receiving mixed messages. The Royal Australian College of General Practitioners has recently released a clinical guideline on drugs of dependence, and practice staff can use this as a reference.[8] Practices may also wish to consider a sign in the waiting room that explains some basic policies (Box 4).[10]

What GPs can do

The practice's approach to prescribing drugs of dependence should be applied universally and without prejudice towards any group of patients. While there are red alerts within a patient's history that may indicate an increased risk of dependence,[11] any person can potentially become addicted to their drugs.

Some GPs find it too difficult to refuse requests for drugs of dependence. The practice policy can help them to say 'no' to such requests. A GP can say 'I don't prescribe drugs of dependence', or 'It is our practice policy not to prescribe drugs of dependence', or 'It is recommended by health guidelines that we do not prescribe these medicines'. Further explanations are not needed. The GP can then suggest that the focus is shifted to seeing what other strategies can be used to help the patient with their presenting problem.

Box 3 Recommended areas for inclusion in a general practice policy on prescribing drugs of dependence

Conditions for GP registrars prescribing drugs of dependence

Handover standards from specialists and secondary care units

First presentations of new patients requesting continuation of drugs of dependence prescribed by another doctor

Managing requests for 'repeat' scripts for drugs of dependence

Appropriate triaging and management of patients who are assessed as high risk (e.g. referral to specialised services)

Adopting a practice standard approach to patients displaying drug-seeking behaviour

Providing standard information on harms and risks to patients who are prescribed drugs of dependence

Setting ceiling limits for opioid prescribing in the practice (above which a review is triggered)

Standards for the 12-month review of patient opioid use – if opioid therapy is required for longer than 12 months, the PBS requires clinical review of the case and support by a second medical practitioner. The standards required for evaluation for the PBS review have not been documented, but the RACGP Clinical Governance Framework provides a sample protocol

Prescription pad security

Staff safety – adopting a zero tolerance to violence towards staff

PBS Pharmaceutical Benefits Scheme RACGP Royal Australian College of General Practitioners

Adapted with permission from The Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part A – Clinical governance framework. Melbourne: RACGP, 2015.[8]

Before an ongoing need for a drug of dependence can be medically justified, a full biopsychosocial assessment needs to be done, contact with the previous treating doctors made, and a treatment plan formulated. Monitoring within frequent review appointments should occur and include assessment of the patient's function and quality of life, and not just resolution of one symptom. All of this should be clearly documented. Most patients receiving drugs of dependence will have complex problems and require collaborative care and hence should be offered a care plan. Care plans can also be used to encourage patients to engage in active approaches to treatment such as goal setting and the identification, and hence prevention of, triggers to drug use.

It is possible for any person to develop a prescription drug dependence and precautions should be built into a practice policy. Controlled prescribing strategies (Box 5) are part of this approach. GPs should discuss the addictive nature of the drugs, the harms that can ensue, and that these drugs will not be prescribed in the long term, but only until other treatment strategies are put in place. It is important to set clear time boundaries from the outset. Such discussions should occur within a patient-centred framework,[12] hence the GP should talk in terms of judging the treatment and not the patient. Practices should also consider using a contract to inform patients about controlled prescribing, boundaries and the risks and benefits of treatment.[13] The wording of such contracts should be focused on promotion of patient well-being and safety, and not primarily used for the protection of the prescriber.

Box 4 Sample text for practice policy on drugs of dependence [10]

Painkiller and sleeping pills policy

Except for terminal cancer, our policy is that we will not prescribe these medicines (e.g. oxycontin and morphine)

- at your first appointment
- on a phone request
- without a proper assessment
- over the long term (we prefer safer and better options)

Box 5 Controlled prescribing strategies

Controlled quantities: Prescribe what is needed and safe. You can prescribe smaller quantities (e.g. 10 tablets) than the standard packaging quantities that automatically come up in the prescribing software. Discuss this with the pharmacist.

Controlled dispensing: Consider setting up arrangements with the patient's local pharmacy so that a small quantity can be dispensed at an interval agreed with the patient. For example, arrange for the patient to attend once or twice a week, or daily. You will need to contact the pharmacist to arrange this and write these dispensing instructions on the prescription.

Private scripts or authority scripts for increased quantities: These should only be used for patients with cancer-related pain or those receiving palliative care.

Request patients obtain their prescriptions from one pharmacy: This encourages an open and communicative approach to management and improves the safety of prescribing.

Obtain a fuller picture of patients' prescriptions outside your practice: Ring the Prescription Shopping Information Service hotline (1800 631 181) with or without a patient's consent, but be aware there are limitations on the information available.

Inform patients that they will need to see the same GP for all reviews associated with their prescription: No telephone requests for extensions or 'lost' scripts will be given.

If patients present with opioid dependency and are not suitable for a trial of controlled prescribing, they can be offered treatment with opioid substitution therapy in the form of methadone or buprenorphine. GPs can become approved prescribers and are well placed to provide holistic primary health care alongside treatment of a patient's dependency.

All practitioners have a duty to act within state, territory and national legislative frameworks (Box 6).[8] There can be medicolegal consequences for not complying.[14]

Conclusion

There is strong evidence that serious harms can result from misuse of prescription drugs of dependence. GPs should be aware of drug-seeking behaviours that may indicate a patient has a dependency problem. All GPs should develop practice policies stating their approach to prescribing drugs of dependence. ◁

Conflict of interest: none declared

Box 6 State and territory legislative frameworks and clinical advisory services

Australian Capital Territory

Legislative framework:
Pharmaceutical Services Section, ACT Health – 02 6205 0998

24-hour clinical advisory service:
Drug and Alcohol Clinical Advisory Service – 03 9418 1082

New South Wales

Legislative framework:
Pharmaceutical Services Unit, NSW Health – 02 9391 9944

24-hour clinical advisory service:
Drug and Alcohol Specialist Advisory Service – 02 9361 8006 (Sydney) 1800 023 687 (rural)

Northern Territory

Legislative framework:
Poisons Control Unit, Department of Health – 08 8922 7341

24-hour clinical advisory service:
Drug and Alcohol Clinical Advisory Service – 1800 111 092

Queensland

Legislative framework:
Medicines and Poisons, Queensland Health – 07 3328 9890

24-hour clinical advisory service:
GPs can phone Alcohol and Drug Information Service – 1800 177 833 to be put through to Alcohol, Tobacco and Other Drugs for clinical advice

South Australia

Legislative framework:
Drugs of Dependence Unit, SA Health – 1300 652 584

24-hour clinical advisory service:
Drug and Alcohol Clinical Advisory Service – 08 8363 8633

Tasmania

Legislative framework:
Pharmaceutical Services Branch, Department of Health and Human Services – 03 6166 0400

24-hour clinical advisory service:
Drug and Alcohol Clinical Advisory Service – 1800 630 093

Victoria

Legislative framework:
Drugs and Poisons Regulation, Department of Human Services – 1300 364 545

24-hour clinical advisory service:
Drug and Alcohol Clinical Advisory Service – 1800 812 804

Western Australia

Legislative framework:
Pharmaceutical Services Branch, Department of Health – 08 9222 6883

24-hour clinical advisory service:
Clinical Advisory Service – 08 9442 5042

REFERENCES

1. Pilgrim JL, Yafistham SP, Gaya S, Saar E, Drummer OH. An update on oxycodone: lessons for death investigators in Australia. Forensic Sci Med Pathol 2015;11:3-12. http://dx.doi.org/10.1007/s12024-014-9624-x
2. Dobbin M. Pharmaceutical drug misuse in Australia. Aust Prescr 2014;37:79-81. http://dx.doi.org/10.18773/austprescr.2014.033
3. Australian Institute of Health and Welfare. National Drug Strategy Household Survey detailed report: 2013. Canberra: AIHW; 2015. www.aihw.gov.au/publication-detail/?id=60129549469&tab=2 [cited 2016 May 1]
4. Holliday S, Hayes C, Dunlop A. Opioid use in chronic non-cancer pain--part 1: known knowns and known unknowns. Aust Fam Physician 2013;42:98-102.
5. Harrison CM, Charles J, Henderson J, Britt H. Opioid prescribing in Australian general practice. Med J Aust 2012;196:380-1. http://dx.doi.org/10.5694/mja12.10168
6. Frei MY, Nielsen S, Dobbin MD, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust 2010;193:294-6.
7. Nicholas R, Lee N, Roche A. Pharmaceutical drug misuse in Australia: complex issues, balanced responses. Adelaide: National Centre for Education and Training on Addiction (NCETA), Flinders University; 2011. http://nceta.flinders.edu.au/files/6113/2823/3742/EN448_Nicholas_2011.pdf [cited 2016 May 1]
8. Royal Australian College of General Practitioners. Prescribing drugs of dependence in general practice, Part A: clinical governance framework. Melbourne: RACGP; 2015. http://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-a [cited 2016 May 1]
9. National pharmaceutical drug misuse framework for action (2012-2015). Canberra: National Drug Strategy; 2013. www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/drug-mu-frm-action [cited 2016 May 1]
10. GP toolkit: 4 step process for opioid prescribing in general practice. Sydney: UNSW Medicine National Drug & Alcohol Research Centre; 2010. https://ndarc.med.unsw.edu.au/content/gp-toolkit [cited 2016 May 1]
11. Opioid risk assessment tool (ORT) assessment instrument. Clinical Tools Inc.; 2015. www.opioidrisk.com/node/887 [cited 2016 May 1]
12. Nicolaidis C. Police officer, deal-maker, or health care provider? Moving to a patient-centered framework for chronic opioid management. Pain Med 2011;12:890-7. http://dx.doi.org/10.1111/j.1526-4637.2011.01117.x
13. Holliday S, Hayes C, Dunlop A. Opioid use in chronic non-cancer pain--part 2: prescribing issues and alternatives. Aust Fam Physician 2013;42:104-11.
14. Jammal W, Gown G. Opioid prescribing pitfalls: medicolegal and regulatory issues. Aust Prescr 2015;38:198-203. http://dx.doi.org/10.18773/austprescr.2015.069

Dental note

Drug-seeking behaviour

Christopher Daly
Chair
Dental Therapeutics Committee
Australian Dental Association

Aust Prescr 2016;39:101
http://dx.doi.org/10.18773/austprescr.2016.029

Dentists should be aware that patients may seek prescriptions for benzodiazepines or opioids in order to misuse or sell those drugs.

Requests for benzodiazepines generally involve new patients who claim to be very apprehensive about dental treatment and who may display anxiety characteristics during their dental examination. They often inform the dentist that their previous dentist always prescribed 'something to calm me down' and that it was 'the only way that the dentist could do any work on me'.

Dentists need to have a level of suspicion when receiving such requests, especially when patients identify drugs by name, or cannot recall or are unwilling to divulge the name and locality of their previous dentist. Contact with the patient's previous dentist or their medical practitioner can assist in identifying the bona fide case from those seeking prescriptions for misuse. Also, prescription of one or two tablets only, rather than a full pack, can be helpful to avoid misuse.

In Australia, the National Drug Strategy Household Survey 2013[1] identified misuse of analgesics as showing the largest increase between 2010 and 2013 of all drug types surveyed. It found that 7.7% of people in 2013 had used them for non-medical purposes compared with 4.8% in 2010. Those seeking to misuse opioids may do so with over-the-counter medicines which combine codeine (12.8 mg) with ibuprofen (200 mg), and also codeine (15 mg) with paracetamol (500 mg). The most commonly misused prescribed opioid in Australia was a combination of codeine and paracetamol.[1] Such combinations consist of codeine (30 mg) and paracetamol (500 mg). These drugs are recommended for the management of severe pain after dental treatment at adult doses of codeine (60 mg) plus paracetamol (1000 mg) given every four hours (to a maximum paracetamol dose of 4 g every 24 hours).[2]

Patients who are seeking opioid prescriptions may claim to have severe dental pain, may present with self-inflicted intra-oral injuries, or may even deliberately irritate extraction sockets or ongoing root canal therapy. Dentists need to be suspicious of patients who wish to have 'drug-only' treatment and either refuse or are not interested in non-drug treatment. The Box shows suggested responses to a patient seeking drugs.

Conflict of interest: none declared

Box Suggested responses to a patient seeking drugs from a dentist

Opioids

'The drugs you are seeking are not appropriate for your particular problem. I think you should discuss this with your medical practitioner (I could contact them if you like), or if your pain is very severe, perhaps you should attend hospital.'

Benzodiazepines

'I do not prescribe the drugs you are seeking. I think you should discuss this with your medical practitioner (I could contact them if you like), or I could refer you to a specialist who manages anxious patients.'

REFERENCES

1. Australian Institute of Health and Welfare. National Drug Strategy Household Survey detailed report: 2013. Canberra: AIHW; 2015. www.aihw.gov.au/publication-detail/?id=60129549469&tab=2 [cited 2016 May 1]
2. Oral and Dental Expert Group. Therapeutic Guidelines: oral and dental. Version 2. Melbourne: Therapeutic Guidelines Limited; 2012.

COMMENT

Meldonium and the WADA Prohibited List

David Hughes
Chief medical officer
Australian Institute of Sport
Medical director
Australian Olympic Team, Rio 2016

Keywords
drug abuse, meldonium, Mildronate, sports activity

Aust Prescr 2016;39:102
http://dx.doi.org/10.18773/austprescr.2016.032
First published online 7 April 2016

Recent developments in sports anti-doping serve to highlight the importance of athletes, sports officials and medical practitioners maintaining a high level of vigilance regarding the use of prescription drugs by athletes. On 7 March 2016, professional tennis player Maria Sharapova announced that she had incurred a positive doping test at the Australian Open Tennis Championships in January, as a result of consuming the banned drug meldonium.

Meldonium (also known by the brand name Mildronate) is produced in Latvia and is available over the counter. It is predominantly used in Latvia, Russia and Eastern Europe. The drug is not approved for use in Australia. Meldonium is reported to have cardioprotective and anti-ischaemic effects. In the vast majority of circumstances, it would be prescribed for elderly individuals with ischaemic conditions.

During 2015 meldonium was on the monitoring program of the World Anti-Doping Agency (WADA).[1] Meldonium was added to the WADA Prohibited List on 1 January 2016 because of evidence of its use by athletes with the intention of enhancing performance.[2] It is thought to improve athletic performance by increasing the capacity for oxygen delivery to peripheral tissues during exercise.[3]

There has been growing evidence of the abuse of meldonium by athletes for performance-enhancing purposes. At the Baku 2015 European Games, only 23 of the 662 (3.5%) athletes tested between 8 and 28 June 2015 declared the personal use of meldonium. This included 13 competition winners. However, 66 (8.7%) of the 762 athletes' urine samples analysed pre-competition and during the Games tested positive for meldonium.[4]

The Prohibited List is reviewed each year by WADA and any decisions to alter it are finalised in September. All relevant anti-doping organisations were informed before 1 October 2015 that meldonium had been added to the Prohibited List with the change coming into effect on 1 January 2016.

Medical practitioners dealing with athletes subject to doping control testing need to be aware of the Prohibited List. Where any doubt exists, medical practitioners can find useful information on the website of the Australian Sports Anti-Doping Authority (ASADA) www.asada.gov.au. In particular, the 'Check Your Substances' page (https://checksubstances.asada.gov.au) provides an easy reference for medical practitioners when there is doubt regarding the status of a particular drug. If any doubt persists and the medical problem is not urgent, the athlete should be urged to consult with their national sporting organisation. All national sporting organisations have appropriate contacts through which they can provide advice. If a medical practitioner, coach, athlete or parent has further questions that cannot be answered via the ASADA website, they can ring ASADA on 1300 027 232. ◁

Conflict of interest: none declared

REFERENCES

1. Hughes D. The World Anti-Doping Code in sport: update for 2015. Aust Prescr 2015;38:167-70. http://dx.doi.org/10.18773/austprescr.2015.059
2. World Anti-Doping Agency. WADA statement regarding Maria Sharapova case. 2016 Mar 7. www.wada-ama.org/en/media/news/2016-03/wada-statement-regarding-maria-sharapova-case [cited 2016 Apr 1]
3. Dzintare M, Kalvins I. Mildronate increases aerobic capabilities of athletes through carnitine-lowering effect. In: 5th Baltic Sport Science Conference: Current issues and new ideas in sports science; 2012 Apr 18-19; Kaunas, Lithuania. Lithuania: Lithuanian Academy of Physical Education; 2012.
4. Stuart M, Schneider C, Steinbach K. Meldonium use by athletes at the Baku 2015 European Games. Adding data to Ms Maria Sharapova's failed drug test case. BMJ Blogs. 2016 Mar 8. http://blogs.bmj.com/bjsm/2016/03/08/meldonium-use-by-athletes-at-the-baku-2015-european-games-adding-data-to-ms-maria-sharapovas-failed-drug-test-case/ [cited 2016 Apr 1]

COMMENT

Farewell to print

NPS MedicineWise has decided that *Australian Prescriber* will not be printed after June 2016. Publication of the journal will continue online through a newly constructed NPS MedicineWise website (nps.org.au/australianprescriber).

As the Editorial Executive Committee has to say farewell to hard copy, it has been reflecting on the history of the printed journal. Much has changed since *Australian Prescriber* was first published in 1975.[1] Back then, the annual cost of the Pharmaceutical Benefits Scheme was approximately $270 million. It has now grown to nearly $10 billion and the general patient copayment has risen from $1.50 to $38.30.

Since 1975 there have been 39 volumes and 190 issues of *Australian Prescriber*. To discuss the content of these issues, the Editorial Executive Committee has held 310 meetings.

Australian Prescriber was first published by the Australian Government Publishing Service. Initially there were four issues of the journal each year. There was a missing issue in 1977 and print publication was halted in mid-1982. Thanks to lobbying by the Executive Editorial Board, publication resumed again in 1983 with the support of the then Federal Minister of Health (see Fig. 1). Originally each volume was individually indexed. From 1990 a five-year cumulative index was published each year. There will be no index in the new online journal.

In 1999, as there was increasing recognition of the importance of independent information in the quality use of medicines, production of *Australian Prescriber* was increased to six issues per year. The National Prescribing Service (now known as NPS MedicineWise) took over responsibility for the publication of *Australian Prescriber* in 2002. It renamed the Executive Editorial Board as the Editorial Executive Committee.

During the past four decades there have been 10 cover designs. Common elements in many designs are medicines and the eye of the Horus. Paper from sustainable sources has been used since 2009.

Australian Prescriber is read by a wide range of health professionals (see Fig. 2). In 2014, a national survey found that more than 96% of health professionals were aware of *Australian Prescriber* and more than 87% were readers of the printed journal.

While the overseas distribution of the printed journal ceased in December 2009, the domestic distribution has been relatively stable at around 53 000 copies.

The Editorial Executive Committee therefore believes that *Australian Prescriber* had the largest circulation of any medical journal in Australia.

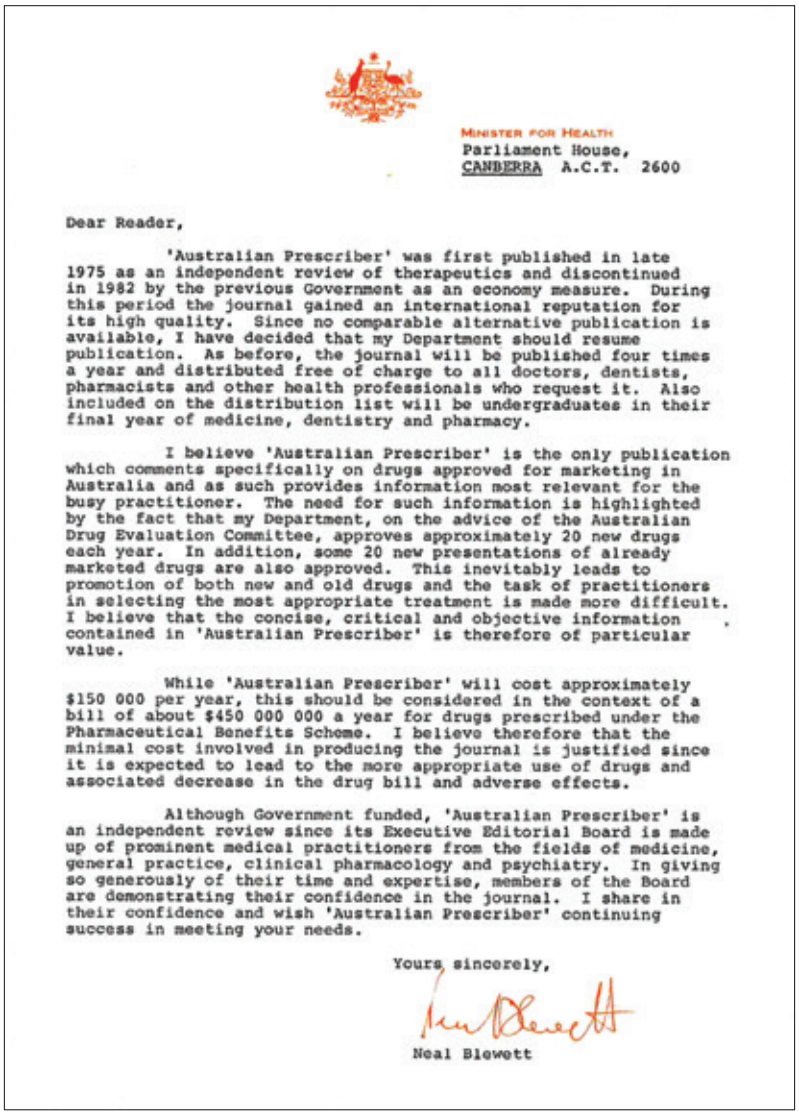
Reading *Australian Prescriber* online is nothing new. In the 1990s the members of the Executive Editorial Board were enthusiastic early adopters of the internet. It is now 20 years since *Australian Prescriber* became one of the first medical journals to be published online. Readers have been able to choose whether to access the journal's content electronically, via print, or both. However, NPS MedicineWise is now directing resources towards electronic access and is therefore discontinuing print publication.[2]

***Australian Prescriber* Editorial Executive Committee**

Keywords
Australian Prescriber, medical journal

Aust Prescr 2016;39:103–4
http://dx.doi.org/10.18773/austprescr.2016.043

Fig. 1 **Letter to readers from the Minister for Health, 1983**



MINISTER FOR HEALTH
Parliament House,
CANBERRA A.C.T. 2600

Dear Reader,

'Australian Prescriber' was first published in late 1975 as an independent review of therapeutics and discontinued in 1982 by the previous Government as an economy measure. During this period the journal gained an international reputation for its high quality. Since no comparable alternative publication is available, I have decided that my Department should resume publication. As before, the journal will be published four times a year and distributed free of charge to all doctors, dentists, pharmacists and other health professionals who request it. Also included on the distribution list will be undergraduates in their final year of medicine, dentistry and pharmacy.

I believe 'Australian Prescriber' is the only publication which comments specifically on drugs approved for marketing in Australia and as such provides information most relevant for the busy practitioner. The need for such information is highlighted by the fact that my Department, on the advice of the Australian Drug Evaluation Committee, approves approximately 20 new drugs each year. In addition, some 20 new presentations of already marketed drugs are also approved. This inevitably leads to promotion of both new and old drugs and the task of practitioners in selecting the most appropriate treatment is made more difficult. I believe that the concise, critical and objective information contained in 'Australian Prescriber' is therefore of particular value.

While 'Australian Prescriber' will cost approximately $150 000 per year, this should be considered in the context of a bill of about $450 000 000 a year for drugs prescribed under the Pharmaceutical Benefits Scheme. I believe therefore that the minimal cost involved in producing the journal is justified since it is expected to lead to the more appropriate use of drugs and associated decrease in the drug bill and adverse effects.

Although Government funded, 'Australian Prescriber' is an independent review since its Executive Editorial Board is made up of prominent medical practitioners from the fields of medicine, general practice, clinical pharmacology and psychiatry. In giving so generously of their time and expertise, members of the Board are demonstrating their confidence in the journal. I share in their confidence and wish 'Australian Prescriber' continuing success in meeting your needs.

Yours sincerely,

Neal Blewett

COMMENT

Farewell to print

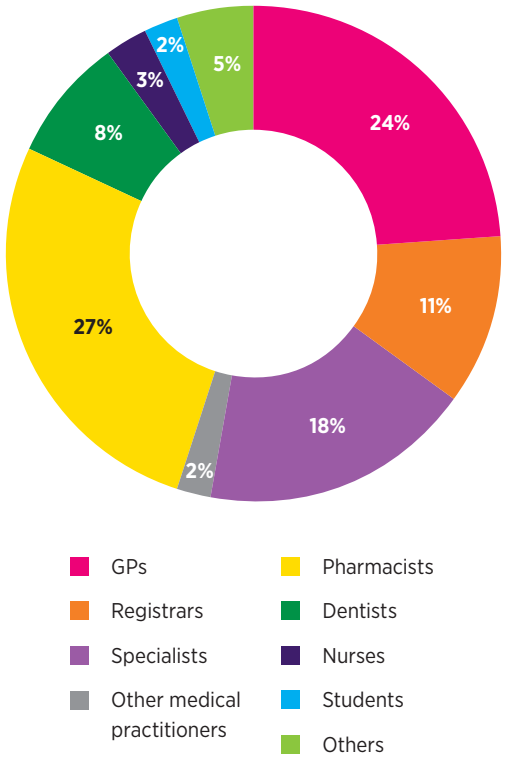
Australian Prescriber has already achieved significant milestones in electronic publishing. It has been listed in the Directory of Open Access Journals since 2003. The journal has been freely available online since 1996 and open access will continue after the cessation of print publication. A website for mobile devices was established in 2013. The first *Australian Prescriber* smartphone app, The Doctor's Bag, was launched in mid-2015. Readers have been able to follow the journal on Twitter @AustPrescriber since 2012.

In late 2015, *Australian Prescriber* was accepted for inclusion in PubMed Central. Digital object identifiers are now assigned to all articles published in the journal, enhancing scholarly citation.[3]

Each month more than 200 000 people visit the *Australian Prescriber* website. More than 22 000 readers already subscribe to email alerts to be notified of the publication of each new issue, and of material published between issues (online first) such as comments on new drugs.

The Editorial Executive Committee of *Australian Prescriber* encourages readers of the printed journal to visit the new website at nps.org.au/australianprescriber. It is our intention that *Australian Prescriber* will remain a free, independent publication providing open access information about drugs and therapeutics to busy health professionals. ◁

Fig. 2 **Australian print categories for April 2016**



REFERENCES

1. Dowden J. Forty and forward? Aust Prescr 2015;38:146-7. http://dx.doi.org/10.18773/austprescr.2015.053
2. Weekes L. The NPS MedicineWise vision for Australian Prescriber [editorial]. Aust Prescr 2016;39:70-1. http://dx.doi.org/10.18773/austprescr.2016.042
3. Exciting things happening in the digital space. Aust Prescr 2016;39:13. http://dx.doi.org/10.18773/austprescr.2016.012

Examples of *Australian Prescriber* front covers from the past


1975–1977


1977–1978


1980


1984–1993


1994–1999


2005


April 2015


October 2015

WEBSITE REVIEW

Website review

Pregnancy and Breastfeeding Medicines Guide

Debra Kennedy
Clinical geneticist
IVF Australia

Director
MotherSafe
Royal Hospital for Women
Sydney

Aust Prescr 2016;39:105
http://dx.doi.org/10.18773/austprescr.2016.034

https://thewomenspbmg.org.au
Melbourne: The Royal Women's Hospital

This website lives up to its description of a quick reference guide for healthcare professionals that provides practical and unbiased specialised information on medicine use in pregnancy and breastfeeding. The online format has replaced the hard copy version which was last published in November 2014.

The guide includes an A–Z listing of over 900 evidence-based individual medicine monographs which support prescribing during pregnancy and breastfeeding. It also includes summaries of therapeutic groups such as antidepressants and antihistamines with general advice about the pharmacological management of common conditions such as nausea and vomiting in pregnancy, and constipation.

One hopes that the online format makes this resource more appealing to pharmacists in the community as it is clearly far superior to other prescribing references such as MIMS. The guide would also be a very useful resource for busy obstetricians in private practice (as well as hospital antenatal clinics).

This guide includes medicines available in Australia but not in the USA (e.g. cyproterone). There is often limited or no information about these drugs in other resources.[1-3]

Annual subscription is $170 making this a little pricier than your average reference book. However, the guide has monthly updates which include information about new drugs, as well as updated data about older medicines or therapeutic groups.

Overall I think this is an excellent resource and congratulate the authors on putting it all together in such a user-friendly format. I would recommend it to all maternity hospitals and community pharmacies to optimise medicine use and prescribing in pregnant and breastfeeding women.

REFERENCES

1. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia (PA): Lippincott Williams and Wilkins; 2011.
2. Reprotox. Washington DC: Reproductive Toxicology Center. https://reprotox.org/ [cited 2016 May 1]
3. TERIS. Teratogen information service. Washington: University of Washington. http://depts.washington.edu/terisdb/index.html [cited 2016 May 1]

NEW DRUGS

New drugs

Ceftolozane sulfate with tazobactam sodium

Aust Prescr 2016;39:106-7
http://dx.doi.org/10.18773/austprescr.2016.044
First published online 18 April 2016

Approved indication: specified infections

Zerbaxa (Merck, Sharp and Dohme)
vials containing 1000 mg/500 mg powder for reconstitution
Australian Medicines Handbook section 5.1.3

Antibiotic resistance is a growing problem. This combination of ceftolozane (a cephalosporin) with tazobactam (a beta-lactamase inhibitor) is an attempt to address multidrug resistant Gram-negative bacteria. These organisms can cause severe intra-abdominal infections and complicated urinary tract infections.

Ceftolozane has a bactericidal action. Its spectrum of activity is extended by combining with tazobactam to inhibit the beta-lactamase enzymes produced by organisms such as *Escherichia coli* and *Klebsiella* species. The combination also has efficacy against bacteria such as *Pseudomonas aeruginosa*, *Enterobacter* and *Proteus mirabilis*. It is not effective for infections caused by *Staphylococcus aureus* or enterococci.

The combination has to be given by intravenous infusion. The reconstituted solution is diluted and infused over an hour every eight hours. Most of the dose is renally excreted, so lower doses are needed in patients with a creatinine clearance below 50 mL/minute. As there is a potential for hypersensitivity reactions, the infusion should be given where there are facilities for managing anaphylaxis.

A multicentre study enrolled patients with pyelonephritis or complicated lower urinary tract infections. One group of 543 was randomised to receive infusions of ceftolozane with tazobactam, while 540 received infusions of levofloxacin (a quinolone). Approximately 74% of the patients had a positive urine culture. Most of them were infected with *E. coli*. Treatment for seven days with the combination eradicated the organisms in 80.4% of patients compared with 72.1% with levofloxacin. There was a clinical cure in 92% of these patients treated with the combination and 88.6% of those given levofloxacin.[1]

Another trial studied patients with complicated intra-abdominal infections such as appendiceal abscess or perforation. A group of 487 patients was randomised to receive ceftolozane/tazobactam and metronidazole, while 506 were randomised to intravenous meropenem. *E. coli* was frequently found, but most of the infections were polymicrobial. Treatment was for 4–10 days, but could continue for 14 days. At the end of therapy there was a clinical cure in 89.2% of the patients treated with the combination and 92.3% of those given meropenem. When the patients were assessed a median of 27 days after the start of therapy, the clinical cure rates were 83% with the combination and 87.3% with meropenem.[2]

In the clinical trials the most frequent adverse events in patients taking the combination of ceftolozane with tazobactam were nausea, headache and diarrhoea. In some cases the diarrhoea was associated with *Clostridium difficile*. Although 12 patients treated with the combination died, none of these deaths were considered to be related to treatment.

There are no studies of the combination in pregnancy. It is also unknown if the drugs are excreted in breast milk.

While the clinical trials show that ceftolozane with tazobactam is effective, the combination should probably be reserved for severe cases where a multidrug resistant organism is suspected. In Australia cephalosporins are not usually first-line drugs. Therapeutic Guidelines[3] recommends that an empirical therapy for severe pyelonephritis is gentamicin with ampicillin or amoxycillin.

T manufacturer provided the product information

REFERENCES *†A

1. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015;385:1949-56. http://dx.doi.org/10.1016/S0140-6736(14)62220-0
2. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 2015;60:1462-71.
3. eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014. http://www.tg.org.au/index.php?sectionid=71 [cited 2016 Apr 11]

A Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

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

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

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

Announcement

Continuing Professional Development

Due to the transition to the new NPS MedicineWise website, continuing professional development (CPD) activities for *Australian Prescriber* articles are not currently available.

Back issues

Back issues of *Australian Prescriber* from the last two years, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, are available in hard copy on request.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True

EDITORIAL OFFICE

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

Postal The Editor
Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

Fax (02) 6282 6855

Email info@australianprescriber.com

Website nps.org.au/australianprescriber

Twitter @AustPrescriber

SUBSCRIPTIONS

Australian Prescriber is published every two months online. All content is accessible free of charge in full text at nps.org.au/australianprescriber. New drugs are published between issues as they become available.

An email alert can be sent to you when *Australian Prescriber* publishes new material. Subscribe or update your details at nps.org.au/australianprescriber

For back issues, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, email info@australianprescriber.com

© NPS MedicineWise
ABN 61 082 034 393

NPS MedicineWise Disclaimer

Reasonable care is taken to provide accurate information at the time of creation. This information is not intended as a substitute for medical advice and should not be exclusively relied on to manage or diagnose a medical condition. NPS MedicineWise disclaims all liability (including for negligence) for any loss, damage or injury resulting from reliance on or use of this information.

Australian Prescriber

EDITORIAL EXECUTIVE COMMITTEE

Chair
A Knight – General physician
Medical editor
JS Dowden
Deputy editor
FG Mackinnon

Members
L Ahmad – Geriatrician
I Coombes – Pharmacist
C Galletly – Psychiatrist
D Roberts – Clinical pharmacologist
T Usherwood – General practitioner

SECRETARIAT AND PRODUCTION

Production manager
G Hickey

Editorial assistant
C Graham

Production coordinator
K McGarry

Office administrator
J Dixon

ADVISORY EDITORIAL PANEL

Australasian Chapter of Addiction Medicine M McDonough
Australasian Chapter of Sexual Health Medicine C Carmody
Australasian College for Emergency Medicine J Holmes
Australasian College of Dermatologists ID McCrossin
Australasian College of Tropical Medicine K Winkel
Australasian Faculty of Occupational and Environmental Medicine R Horsley
Australasian Faculty of Rehabilitation Medicine G Bashford
Australasian Society for HIV Medicine J Ziegler
Australasian Society for Infectious Diseases A Watson
Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists J Martin
Australasian Society of Clinical Immunology and Allergy C Katelaris
Australian and New Zealand Association of Neurologists F Vajda
Australian and New Zealand College of Anaesthetists K Brandis
Australian and New Zealand Society for Geriatric Medicine S Johns
Australian and New Zealand Society of Blood Transfusion J Isbister
Australian and New Zealand Society of Nephrology P Snelling
Australian and New Zealand Society of Palliative Medicine F Formby
Australian Birth Defects Society D Kennedy
Australian College of Nurse Practictioners J O'Connell
Australian College of Rural and Remote Medicine A Iannuzzi
Australian Dental Association C Daly
Australian Medical Association J Gullotta
Australian Pharmaceutical Medical and Scientific Professionals Association K Hargreaves
Australian Rheumatology Association J Bertouch
Australian Society of Otolaryngology Head and Neck Surgery EP Chapman
Cardiac Society of Australia and New Zealand JHN Bett
Consumers Health Forum of Australia M Metherell
Endocrine Society of Australia RL Prince
Gastroenterological Society of Australia P Desmond
Haematology Society of Australia and New Zealand F Firkin
High Blood Pressure Research Council of Australia LMH Wing
Internal Medicine Society of Australia and New Zealand M Kennedy
Joint Health Command, Australian Defence Force RG Beran
Medical Oncology Group of Australia SJ Clarke
National Heart Foundation of Australia J Tatoulis
Pharmaceutical Society of Australia W Plunkett
Royal Australasian College of Dental Surgeons PJ Sambrook
Royal Australasian College of Medical Administrators A Robertson
Royal Australasian College of Physicians N Buckley (adult division)
CM Mellis (paediatric division)
Royal Australasian College of Surgeons M Westcott
Royal Australian and New Zealand College of Obstetricians and Gynaecologists M Hickey
Royal Australian and New Zealand College of Ophthalmologists M Steiner
Royal Australian and New Zealand College of Psychiatrists F Wilson
Royal Australian and New Zealand College of Radiologists P Carr
Royal Australian College of General Practitioners J Smith
Royal College of Pathologists of Australasia JM Potter
Society of Hospital Pharmacists of Australia C Alderman
Thoracic Society of Australia and New Zealand
Urological Society of Australia and New Zealand R Millard

AUSTRALIAN PRESCRIBER IS INDEXED AND ARCHIVED BY

- Academic Search Complete
- Academic Search Research and Development
- Australian Public Affairs Information Service - Health
- EMBASE/Excerpta Medica
- Emerging Sources Citation Index
- PubMed Central

The views expressed in this journal are not necessarily those of the Editorial Executive Committee or the Advisory Editorial Panel.

Apart from any fair dealing for the purposes of private study, research, criticism or review, as permitted under the Copyright Act 1968, or for purposes connected with teaching, material in this publication may not be reproduced without prior written permission from the publisher.

Print Post Approved PP349181/00151 • ISSN 0312-8008
Typesetting by Stripe Design, Canberra
Printing and distribution by CanPrint Communications, Canberra

© 2016 NPS MedicineWise • ABN 61 082 034 393

Published by NPS MEDICINEWISE

Independent, not-for-profit and evidence based, NPS MedicineWise enables better decisions about medicines and medical tests. We receive funding from the Australian Government Department of Health.