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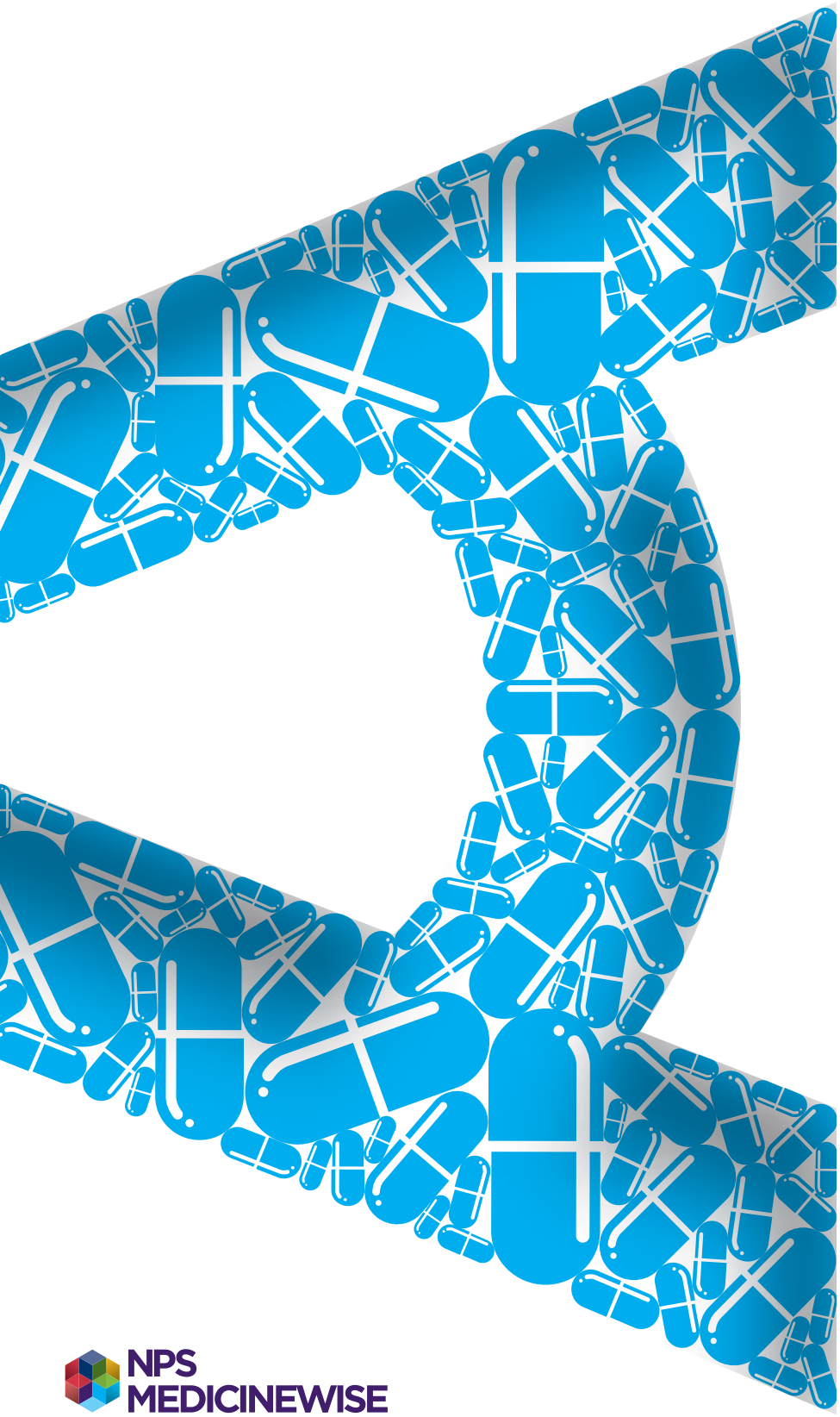

NPS MEDICINEWISE

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EDITORIAL

Are prescription copayments compromising patient care?

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Key words
cost of drugs, Pharmaceutical Benefits Scheme

Aust Prescr 2013;36:2–3

In 2011, around 240 million prescriptions were dispensed on the Australian Pharmaceutical Benefits Scheme (PBS) at a cost of $8.3 billion to the government and a further $2 billion in patient copayments to the pharmacies. The copayment is the price paid by a patient for a prescription.[1] It has evolved over the years and now seems to lack a purpose other than offsetting the cost to government.

In 2013, patient copayments are $36.10 for each prescription or $5.90 if the patient has a concession status. These charges are reduced once a family's expenses in one year reach a safety net threshold. Currently, these thresholds are $1390.60 for general and $354 for concessional patients. The copayments and safety net thresholds are adjusted for inflation every January.

Most general practitioners and community pharmacists are well aware that some patients have difficulty paying for their prescriptions. While copayment increases may reduce what the government pays for medications, they also have unintended effects on patients and elsewhere, for example on the hospital system.

Increases in copayments primarily affect vulnerable populations such as those on low incomes and patients with chronic medical conditions taking multiple medications. To deal with increased costs, patients often reduce or stop taking their medicines and this can have potentially serious health consequences.[2] This failure to take medicines can also lead to increased visits to the doctor and hospitalisations.[3]

There is a relationship between patient cost sharing, medication adherence and clinical and economic outcomes. Increasing the patient's share of medication costs is associated with a decrease in adherence, which in turn is associated with poorer health outcomes.[4] Tiered prescription copayments (similar to brand price premiums and therapeutic group premiums) shift use from 'nonpreferred' to the lower cost 'preferred' medications.[5]

Some have argued that greater cost sharing does not undermine overall patient health because patients facing rising costs will reduce their consumption of perceived non-essential medications more than their consumption of essential drugs.[6] However, 'preventive' drugs are different, because not all patients understand the long-term benefits of taking medicines for conditions such as hypertension and hypercholesterolaemia. In this case, underutilisation may be the problem and 'too much' cost sharing could lead to a loss of clinical benefit.[6] For example, in the USA when copayments were increased from $6 to $10 there was a 6% increase in non-adherence and a 9% reduction in full adherence in patients with type 2 diabetes.[7]

According to the Australian Bureau of Statistics, 9% of adults will delay or not collect their prescriptions.[8] In addition, both non-adherence and poor persistence with long-term treatment are well documented in Australia.[9] One of the major reasons (but not the only reason) for patients failing to collect their medicines is the relatively large out-of-pocket costs of the prescriptions. These costs can become prohibitive if patients are taking multiple drugs.

Evidence is emerging that more patients are failing to collect their prescriptions. Industry data on prescribing of a third-line 'add-on' antihypertensive drug showed that towards the end of 2011, the

From the Editor

The first issue of 2013 could be controversial. The papers on calcium, chemotherapy, convulsive therapy, competency and copayments are certainly thought-provoking and could change practice.

Calcium supplements are widely promoted and prescribed for bone health. While some patients may benefit, Mark Bolland, Andrew Grey and Ian Reid believe that widespread use of calcium is no longer appropriate as the supplements can increase the risk of cardiovascular events.

The use of oral cytotoxic drugs is increasing. Although patients can now be treated at home, there are risks and Christine Carrington advises how to minimise the potential harm.

There is also increasing use of biological medicines in the community. Sateesh Shankaranarayana, Claire Barrett and Paul Kubler review the safety of leflunomide.

Concerns about the safety of lithium have limited its use, but Gin Malhi, Michelle Tanious, Danielle Bargh, Pritha Das and Michael Berk say it is well tolerated if prescribed wisely. Although it is not heavily promoted, lithium is an effective treatment for bipolar disorder.

Some patients with depression will require electroconvulsive therapy. Colleen Loo tells us that the new technique of ultrabrief pulse stimulation could reduce the cognitive adverse effects of this treatment.

Safe treatment requires health professionals to be competent in what they do. Elaine Lum, Charles Mitchell and Ian Coombes consider how to assess the competencies of Australian prescribers.

proportion of prescriptions dispensed on the PBS had declined relative to the number of prescriptions written by general practitioners.

Compared to 2010 the percentage change in concessional prescriptions was consistent with a reduced rate of dispensing from about August 2011. The change in concessional dispensing was also apparent with other antihypertensives. This suggests that concessional copayments may have been too high and fewer patients reached the safety net threshold. (Patients had to pay an extra $12 to reach the concessional safety net in 2011).

Even though the PBS has reduced the price of many commonly prescribed medicines, the cost to concessional patients did not change, because their copayment remains the same. In contrast, general patients derived significant savings from the lower prices, but only if their drugs were priced under the general copayment.

The current fixed copayment system has been around for more than 25 years and with all the PBS reforms taking place, it may be time to take a closer look at patient copayments. The current approach to PBS savings is that the government takes most of the cost savings, but increases copayments and safety net thresholds each year in line with inflation. Increasing copayments reduces medication adherance and ultimately may compromise the care of some patients.

Dr Ortiz is an independent pricing and reimbursement consultant to several pharmaceutical companies.

REFERENCES

1. Tatchell M. Prescription pricing demystified. Aust Prescr 2009;32:6-8.
2. Hynd A, Roughead EE, Preen DB, Glover J, Bulsara M, Semmens J. The impact of co-payment increases on dispensings of government-subsidised medicines in Australia. Pharmacoepidemiol Drug Saf 2008;17:1091-9.
3. Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, et al. Unintended consequences of caps on Medicare drug benefits. N Engl J Med 2006;354:2349-59.
4. Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes: a literature review. P T 2012;37:45-55.
5. Rector TS, Finch MD, Danzon PM, Pauly MV, Manda BS. Effect of tiered prescription copayments on the use of preferred brand medications. Med Care 2003;41:398-406.
6. Lozada C. Effects of co-payment on prescription drug demand. National Bureau of Economic Research; 2005. www.nber.org/digest/apr05/w10738.html [cited 2013 Jan 7]
7. Dor A, Encinosa W. Does cost sharing affect compliance? The case of prescription drugs. National Bureau of Economic Research Working Paper No. 10738. 2004. www.nber.org/papers/w10738 [cited 2013 Jan 7]
8. Australian Bureau of Statistics. Year Book Australia 2012. Canberra: ABS; 2012.
9. Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004-2006. Med J Aust 2008;188:224-7.

Letters to the Editor

Error in compounding imiquimod 0.1% cream for molluscum

Editor, – Imiquimod 5% cream (Aldara) is available in single use 250 mg sachets for genital warts and basal cell carcinoma. For some years, doctors have been prescribing imiquimod 'off-label' for the treatment of molluscum contagiosum in children. Because of the cost ($150–200 for 12 sachets) it is usually prescribed as compounded imiquimod 0.1% cream. To make this, one sachet of imiquimod 5% cream can be diluted 50-fold to 12.5 g of 0.1% cream.

I have seen four children who had been prescribed imiquimod 0.1% which was compounded incorrectly by three separate pharmacies. Each pharmacist had incorrectly assumed that the label '250 mg' on the packaging refers to the quantity of the active ingredient – imiquimod – in the sachet. In fact, it refers to the quantity of 5% cream.

As each dispensed jar of cream is labelled 'imiquimod 0.1%', clinicians need a high index of suspicion to detect this error. They will need to confirm with the patient how much cream was given and what it cost. For example, if a patient received a 250 g jar of '0.1% cream' for $49.95 (as in one of my cases), it is clear an error has been made as this would otherwise contain several hundred dollars worth of imiquimod.

Some months after it began being routinely used for molluscum treatment in Melbourne, imiquimod 0.1% was described to me as 'working well' and 'effective' in many children. To my knowledge, all those children had received their compounded cream from one pharmacy and the dilution was incorrect. As such they had only received imiquimod 0.005%, a 1 in 1000 dilution of the commercially available product. It is unlikely that this was effective and illustrates the difficulty of assessing treatments for molluscum. Molluscum lesions often flare (and hence present to the doctor) shortly before complete resolution so that clearing

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

LETTERS

after presentation is common whatever treatment is used.

Rod Phillips
Paediatric skin specialist
Royal Children's Hospital
Melbourne

Opioids and constipation

Editor, – I refer to the article by Dr McDonough (Aust Prescr 2012;35:20-4). I was interested to see in Table 1 that he recommends non-osmotic laxatives to treat chronic constipation and I wondered why this recommendation is made.

Barry Werth
Faculty of Pharmacy
The University of Sydney

Michael McDonough, author of the article, comments:

Thank you for this important question concerning constipation. The recommendation pertains to chronic opioid-related constipation, which is often difficult to manage because of opioid-induced hypomotility. While the use of stimulant laxatives has been suggested,1 the possibility of longer-term adverse consequences (for example melanosis coli) probably should limit their use, if not exclude them. Regarding the use of bulking agents and osmotic and non-osmotic products, there appears to be limited evidence supporting which is the safest and most effective for long-term use.2 However in my clinical experience, osmotic products can cause problems – for example dehydration and electrolyte disturbance. Many patients experience occasional nausea and vomiting, and are often taking multiple medications.

I therefore recommend the strategy of least risk, that is fluids, bulking agents and non-osmotic products like stool softeners in conjunction with diet, exercise and bowel hygiene counselling. If such management fails, referral to a specialist should be considered. That process may include a review of why such commonly recommended management has apparently failed and then starting a trial of osmotic products with ongoing monitoring of safety and efficacy.

REFERENCES

1. Goodheart CR, Leavitt SB. Managing opioid-induced constipation in ambulatory-care patients. Pain Treatment Topics. 2006. http://pain-topics.org/pdf/Managing_Opioid-Induced_Constipation.pdf [cited 2013 Jan 7]
2. Selby W, Corte C. Managing constipation in adults. Aust Prescr 2010;33:116-9.

Antivenom

Editor, – Your article on antivenom (Aust Prescr 2012;35:152-5) updates all physicians working in emergency departments in areas where envenomation cases are likely to be treated.

Most antivenoms have been removed from our rural emergency room. Given your wide readership, it would perhaps have been beneficial for smaller centres, which now have no antivenom, if the article had mentioned the change in policy on treatment, transport and stabilisation of patients in isolated, non-resourced centres.

Martes Alison
General practitioner
Trundle, NSW

Nick Buckley and Ian Whyte, the authors of the article, comment:

Management of snakebite in remote areas, particularly those without 24-hour laboratory facilities, presents many challenges. Point-of-care tests (for example iSTAT INR and d-dimer) do not substitute for laboratory studies and should not be used under any circumstances. The '20 minute whole blood clotting test' may detect coagulopathy, but requires small clean glass tubes. Even if these are available, in practice the test often will not detect envenomation. Most patients with suspected or confirmed snakebite should therefore be transferred to a larger hospital (with a pressure bandage on the bite and immobilisation) for diagnosis and monitoring.

Most remote hospitals will still be recommended to keep a minimal stock of antivenom. For symptomatic patients, a decision may be made to administer antivenom before or during transfer without laboratory confirmation. Weak evidence suggests early antivenom may reduce the incidence of some complications such as myotoxicity, but at the cost of potential adverse effects from the antivenom (if the patient is not envenomed). This should only be done if the doctor is prepared to treat anaphylaxis.

The NSW Health's snakebite guidelines recommend stocking of antivenom in Trundle (and the NSW Therapeutic Advisory Group lifesaving drugs register recommends that it is available). It is concerning if it is not, for it follows there is no current quick and reliable means of determining where the nearest hospital is with antivenom stocks.

This is another example of the urgent need for a national policy on stocking antidotes and a regularly audited antidote register with a search tool to locate them in an emergency.

ARTICLE

Calcium and cardiovascular risks

SUMMARY

Co-administered calcium and vitamin D supplements prevent fractures in institutionalised elderly women, but there is little evidence that the supplements, administered as monotherapies or in combination, prevent fractures in other people in the community.

Calcium and vitamin D supplements are not always necessary for bisphosphonates to be effective. Individuals at high risk for vitamin D deficiency should be treated with vitamin D supplements before zoledronic acid is prescribed.

There is little evidence that dietary calcium intake is associated with risk of fracture or cardiovascular events, so dietary calcium generally does not require close scrutiny.

Calcium supplements increase the risk of myocardial infarction by about 25% and stroke by 15–20%. The co-administration of vitamin D does not mitigate these risks. Widespread use of calcium supplements to prevent fractures is therefore no longer appropriate.

Introduction

Calcium and vitamin D supplements are commonly recommended for the treatment or prevention of osteoporosis and for patients taking bisphosphonate treatment. These strategies need to be reconsidered as recent evidence suggests that calcium supplements are only marginally effective in preventing fractures, and increase cardiovascular risk.

Skeletal benefits of calcium with or without vitamin D

In 1992 a trial reported that co-administered calcium and vitamin D significantly reduced the risk of hip and non-vertebral fracture in institutionalised elderly women with low dietary calcium intake and a very high prevalence of vitamin D deficiency.[1] However, for other people living in the community the evidence for the benefit of calcium or vitamin D supplements on fracture prevention is less clear. Meta-analyses of randomised controlled trials found that calcium supplements used as monotherapy marginally reduced the risk of total fracture,[2] but increased the risk of hip fracture[3]. Vitamin D supplements used as monotherapy had no effect on total fracture[4,5] and had no effect[5] or marginally increased[4] the risk of hip fracture. The addition of vitamin D to calcium supplements did not change these findings. Calcium with vitamin D marginally reduced the risk of total fracture[2] but did not prevent hip fractures[4,5].

There are several explanations why calcium and vitamin D prevent fractures in vitamin D deficient, frail, elderly women, but not in other people. The benefits seen in elderly women[1] may have arisen from correcting vitamin D deficiency and resulting osteomalacia, which is uncommon in younger people. Another possible explanation is that compliance with calcium supplements is poor (approximately 40–60% in randomised controlled trials[6-8]), which may reduce their effectiveness.

Are calcium and vitamin D supplements necessary when prescribing bisphosphonates?

In clinical trials of osteoporosis treatment, calcium and vitamin D supplements have routinely been co-administered. This has led to suggestions that bisphosphonates are only effective when co-prescribed with calcium and vitamin D, but other trials suggest this is incorrect.

The effects of alendronate on bone density were the same as alendronate plus calcium supplements in a two-year randomised controlled trial in women with dietary calcium intake of more than 800 mg/day.[9] The decreases in bone turnover and improvements in bone density with zoledronate were similar regardless of whether calcium and vitamin D were co-prescribed[10,11] or not[12]. Without calcium and vitamin D, clodronate decreased the risk of fractures by 20% in elderly women.[13] This evidence shows that bisphosphonates used without calcium and vitamin D effectively decrease bone turnover, improve bone density, and prevent fractures.

Co-prescribing calcium and vitamin D to patients taking bisphosphonates is probably unnecessary for most people. An important caveat is that vitamin D deficiency is common in frail elderly patients (in whom osteoporosis is also common). Infusion of zoledronic acid into patients with vitamin D deficiency can provoke significant hypocalcaemia so the deficiency should be corrected before treatment.

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Key words
bisphosphonate, myocardial infarction, osteoporosis, stroke, vitamin D

Aust Prescr 2013;36:5–8

Cardiovascular effects of calcium supplements

The first evidence for the adverse cardiovascular effects of calcium supplements in non-uraemic patients came from our five-year randomised controlled trial of calcium monotherapy in 1471 healthy postmenopausal women. There were increases in cardiovascular event rates in the women allocated to calcium (23.3 vs 16.3 events/1000 patient-years, p=0.043), but the size of the study and number of cardiovascular events meant that the results were not definitive.[14]

Further randomised controlled trials of calcium to address the concern were not practical as the primary endpoint would be one of harm. We therefore undertook a meta-analysis of unpublished cardiovascular data from randomised controlled trials. The lead authors of five trials provided patient-level data, and trial-level data on cardiovascular events were available for 11 trials. Meta-analyses showed that calcium supplements increased the risk of myocardial infarction by approximately 30%. There were also smaller, statistically non-significant, increases in mortality, the risk of stroke and in a composite cardiovascular endpoint.[15]

Co-administered calcium and vitamin D

The findings of our meta-analysis related to calcium supplements used as monotherapy, whereas the use of calcium with vitamin D is more common in clinical practice. The Women's Health Initiative calcium and vitamin D trial, a seven-year randomised controlled trial in more than 36 000 postmenopausal women, had previously reported that calcium and vitamin D did not alter cardiovascular risk.[16] An unusual feature of this trial was that personal, non-protocol use of the trial medications was permitted. The majority of the participants were taking their own calcium supplements at randomisation. Widespread personal use of calcium in the trial might have obscured an adverse effect of calcium supplements on cardiovascular risk.

We re-analysed the data from the trial comparing the effects of calcium and vitamin D in non-users and users of personal calcium. In women who were not taking their own calcium at baseline but were allocated to take calcium and vitamin D in the trial, there were increases in the risk of cardiovascular events of similar magnitude to those in the previous meta-analysis of calcium monotherapy. However, in women who were already taking personal calcium supplements, taking calcium with vitamin D in the trial had no effect on cardiovascular risk.[17] The results suggested that the widespread use of personal calcium supplements in the Women's Health Initiative trial had obscured the adverse cardiovascular effects of calcium with vitamin D.

We then pooled the data from the women not using personal calcium supplements in the Women's Health Initiative trial with all other randomised controlled trials of calcium with vitamin D for which cardiovascular data were available. In this analysis, calcium with vitamin D increased the risk of myocardial infarction by 21% and stroke by 20%.[17]

Calcium with or without vitamin D

We pooled our two meta-analyses of calcium monotherapy and calcium with vitamin D, to determine the effect of calcium with or without vitamin D on cardiovascular risk. Calcium or calcium with vitamin D increased the risk of myocardial infarction by 25% and stroke by 15–19%. Based on these meta-analyses, in 1000 people treated for five years, calcium or calcium with vitamin D would cause six heart attacks or strokes and prevent three fractures.[17]

These findings are consistent with studies of patients with renal impairment, in whom calcium supplements accelerate vascular calcification and increase mortality, in both dialysis and pre-dialysis populations.[18-20] A more recent randomised controlled trial of sunlight exposure to raise vitamin D concentrations in Australian nursing home residents also found that the addition of calcium supplements to sunlight exposure was associated with increases in all-cause and cardiovascular mortality.[21,22]

Given the widespread use of calcium and its presumed safety, it is unsurprising that these unexpected findings have not been universally accepted, although few substantive criticisms have been raised.[23] Misclassification of other events as heart attacks was suggested as a possible explanation, but the increased risk is consistent whether events were self-reported, obtained from hospital discharges, death certificates or independently adjudicated. Others have suggested that the results are not valid because the trials were not primarily designed to assess cardiovascular events. This reasoning would make it impossible to ever detect unexpected adverse events. Others have suggested that more evidence is required before practice should be changed. However, there are no ongoing trials large enough to influence the results from the current meta-analyses, future trials are unlikely given the potential for harm from participating, and results of observational studies will not outweigh the Level 1 evidence from a systematic review of randomised controlled trials. Decisions about the use of calcium supplements must therefore be based on these current data.

Mechanisms

A cause for the increased cardiovascular risk remains unclear. The consistency of the results for calcium monotherapy and calcium and vitamin D suggests that the effect is caused by calcium supplements, and is not mitigated by the co-administration of vitamin D. One possible mechanism is that calcium supplements abruptly increase serum calcium.[24] Higher serum calcium concentrations are associated with many measures of atherosclerosis such as carotid artery plaque thickness[25] and aortic calcification.[26] They are also associated with the incidence of myocardial infarction[27-29] and mortality[30]. It is possible that the rapid increases in serum calcium after taking a calcium supplement may alter vascular calcification and other pathophysiological processes occurring at the blood vessel surface.

Should dietary calcium be recommended in place of calcium supplements?

There are no randomised controlled trials that have evaluated the effect of increasing dietary calcium on either fracture incidence or cardiovascular outcomes. Several observational studies have addressed this topic, although the interpretation of observational studies is difficult. Causality cannot be inferred, confounding is difficult to assess and control for, and the total calcium intake of people taking calcium supplements is usually much greater than the intake achieved through diet alone. With these caveats in mind, there is little evidence that levels of dietary calcium intake are associated with cardiovascular risk.[31-36] Similarly, meta-analyses of observational studies do not suggest that levels of calcium intake are associated with subsequent risk of fracture.[37]

Implications for practice

For the majority of patients, the weak effects that calcium supplements have on fracture risk are outweighed by the increased cardiovascular risk. Recommendations for the widespread use of calcium supplements are no longer appropriate and should be reconsidered.

The one population group in which there is clear evidence of fracture prevention with calcium and vitamin D is the institutionalised frail elderly with a high prevalence of vitamin D deficiency. In this population, however, there is also evidence that the addition of calcium supplements to sunlight exposure increases mortality, so the balance of harm and benefit currently remains uncertain. Routine vitamin D supplementation to prevent osteomalacia is reasonable in this group.

There is little evidence that levels of dietary calcium intake are associated with risk of fracture, and so dietary calcium intake does not require close scrutiny for most people. Patients at high risk of fracture should be encouraged to take drugs with proven efficacy in preventing vertebral and non-vertebral fractures. For bisphosphonates, calcium and vitamin D do not need to be routinely co-prescribed, although patients at high risk of vitamin D deficiency should be prescribed vitamin D supplements. ◁

Professor Reid has received research funding, speaker and consultancy fees from Novartis, Merck and Amgen.

Recommendations for the widespread use of calcium supplements are no longer appropriate and should be reconsidered

Q:

SELF-TEST QUESTIONS

True or false?

1. Calcium supplementation reduces cardiovascular risk.
2. Bisphosphonates do not work without calcium supplements.

Answers on page 35

REFERENCES

1. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.
2. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657-66.
3. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. Osteoporos Int 2008;19:1119-23.
4. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2009:CD000227.
5. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 2010;340:b5463.
6. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621-8.
7. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med 2006;166:869-75.
8. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al. Randomized controlled trial of calcium in healthy older women. Am J Med 2006;119:777-85.
9. Bonnick S, Broy S, Kaiser F, Teutsch C, Rosenberg E, DeLucca P, et al. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. Curr Med Res Opin 2007;23:1341-9.
10. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
11. McClung M, Miller P, Recknor C, Mesenbrink P, Bucci-Rechtweg C, Benhamou CL. Zoledronic acid for the prevention of bone loss in postmenopausal women with low bone mass: a randomized controlled trial. Obstet Gynecol 2009;114:999-1007.
12. Grey A, Bolland M, Wattie D, Horne A, Gamble G, Reid IR. Prolonged antiresorptive activity of zoledronate: a randomized, controlled trial. J Bone Miner Res 2010;25:2251-5.
13. McCloskey EV, Beneton M, Charlesworth D, Kayan K, deTakats D, Dey A, et al. Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. J Bone Miner Res 2007;22:135-41.
14. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. BMJ 2008;336:262-6.

15. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.
16. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:846-54.
17. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
18. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478-83.
19. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007;71:438-41.
20. Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. Kidney Int 2007;72:1255-61.
21. Reid IR, Bolland MJ, Sambrook PN, Grey A. Calcium supplementation: balancing the cardiovascular risks. Maturitas 2011;69:289-95.
22. Sambrook PN, Cameron ID, Chen JS, Cumming RG, Durvasula S, Herrmann M, et al. Does increased sunlight exposure work as a strategy to improve vitamin D status in the elderly: a cluster randomised controlled trial. Osteoporos Int 2011;23:615-24.
23. Reid IR, Bolland MJ, Avenell A, Grey A. Cardiovascular effects of calcium supplementation. Osteoporos Int 2011;22:1649-58.
24. Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparations. Aust N Z J Med 1986;16:193-7.
25. Rubin MR, Rundek T, McMahon DJ, Lee HS, Sacco RL, Silverberg SJ. Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. Atherosclerosis 2007;194:426-32.
26. Bolland MJ, Wang TK, van Pelt NC, Horne AM, Mason BH, Ames RW, et al. Abdominal aortic calcification on vertebral morphometry images predicts incident myocardial infarction. J Bone Miner Res 2010;25:505-12.
27. Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. J Clin Epidemiol 1997;50:967-73.
28. Jorde R, Sundsfjord J, Fitzgerald P, Bønaa KH. Serum calcium and cardiovascular risk factors and diseases: the Tromsø study. Hypertension 1999;34:484-90.
29. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2008;156:556-63.
30. Leifsson BG, Ahren B. Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab 1996;81:2149-53.
31. Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. Lancet 1973;1:1465-7.
32. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 1999;149:151-61.
33. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke 1999;30:1772-9.
34. Ascherio A, Rimm EB, Hernán MA, Giovannucci EL, Kawachi I, Stampfer MJ, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 1998;98:1198-204.
35. Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr 2003;77:814-8.
36. Van der Vijver LP, van der Waal MA, Weterings KG, Dekker JM, Schouten EG, Kok FJ. Calcium intake and 28-year cardiovascular and coronary heart disease mortality in Dutch civil servants. Int J Epidemiol 1992;21:36-9.
37. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 2007;86:1780-90.

Book review

Therapeutic Guidelines: Toxicology and Wilderness. Version 2.

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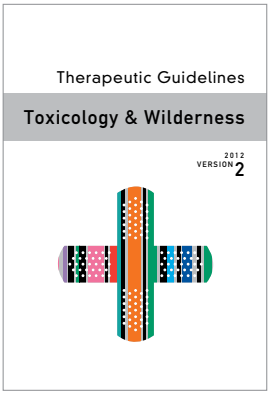

Melbourne: Therapeutic Guidelines Limited; 2012. 303 pages

These guidelines aim to present a comprehensive but succinct review based on current evidence and opinion. Topics are arranged by diagnostic entities and include explicit management recommendations.

I found the book well organised. The expert group of authors are well regarded and the guidelines accurately reflect the most up-to-date information available. The use of key point boxes and lists of further readings give the reader the option of how much detail they want to read. However, these features were not present in all sections.

The book has some minor shortcomings. A toxicology topic on local anaesthetics would have been useful as they are widely used particularly in primary care. A discussion on the role of magnesium in Irukandji syndrome is also warranted, despite the controversy over the evidence, as it is still commonly used in certain situations.

This latest edition covers all the key topics in the field in an easily accessible reference format while still providing enough detail to guide specific therapeutic interventions. Clinicians should find it a useful portable guide.

ARTICLE

Safe use of oral cytotoxic medicines

SUMMARY

The oral route is increasingly used to administer cytotoxic therapy for cancer and non-cancer conditions.

Oral cytotoxic therapy carries the same risk of medication errors as parenteral therapy.

It is essential that health professionals involved in providing oral cytotoxic therapies understand how they are used, what adverse effects can occur and how to minimise medication errors.

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Key words
capecitabine, methotrexate

Aust Prescr 2013;36:9–12

Introduction

Oral administration of cytotoxic therapy has increased over the past decade as newer drugs and formulations have become available (see Table). Cytotoxic chemotherapy is not restricted to cancer. Conditions including rheumatoid arthritis, psoriasis and other autoimmune diseases may be managed using oral medicines such as methotrexate.

The pros and cons of oral cytotoxic therapy

The oral route offers many advantages over the parenteral route of administration. Medicines can be administered in the community, without the need for venous access, and fewer visits to the hospital are needed.

While self-administration at home is convenient for both patients and carers, it can present a risk for the patient. Adverse effects can go undetected unless appropriate steps are in place to monitor the patient. Cytotoxic chemotherapy has a narrow therapeutic index and a small increase in dose can result in toxic effects, while under-dosing can lead to failure of therapy. Serious toxicities and fatal outcomes have occurred as a result of incorrect prescribing and dispensing as well as patient misinterpretation of dosing instructions.[1-6]

Responsibilities of the healthcare team

The safe delivery of oral cytotoxic therapy requires a multidisciplinary approach. Patients may be managed under shared-care arrangements between hospital specialists, general practitioners and community pharmacies.

All health professionals involved should:

- have appropriate training and skills in the use of cytotoxic chemotherapy and cancer care, when therapy is being used in this context[7]
- seek advice from a practitioner experienced in cytotoxic chemotherapy when required
- follow the principles of safe medication practices for oral cytotoxic medicines.

All patients should have a treatment plan. This is completed by the specialist who initiates the treatment[7] and should be given to the patient and all the healthcare professionals involved in their treatment. It is important that the patient has the plan with them if they see a different doctor, for instance in an emergency.

For the treatment plan to be useful, it should be explicit about:

- the patient's diagnosis
- the name of the chemotherapy protocol or specific cytotoxic medicine
- the expected number of cycles and the intended duration of treatment
- other adjuvant or concurrent treatments the patient is receiving (for example radiation therapy or surgery for cancer patients)
- expected adverse effects and their management.

Prescribing

Prescriptions for oral cytotoxic therapy should be clear and unambiguous. The term 'as directed' must not be used regardless of how long the patient has been on the therapy.

Table **Oral cytotoxic medicines**

Drug class	Drugs
Alkylating agents	busulfan, chlorambucil, cyclophosphamide*, lomustine, melphalan, procarbazine, temozolomide
Anthracyclines	idarubicin
Antimetabolites	capecitabine, fludarabine, hydroxyurea*, mercaptopurine*, methotrexate*, thioguanine
Podophyllotoxins	etoposide
Vinca alkaloids	vinorelbine

* currently used for both cancer and non-cancer indications

Prescriptions should specify:

- the generic drug name, number of tablets to be taken[7] and frequency and duration of therapy (written in full)
- whether the medicine is given on a cyclical or continuous basis. For example, capecitabine is frequently administered for 14 days of a 21-day cycle while temozolomide may be administered for 5 days of a 28-day cycle. The start and stop dates for a cycle should be clear.
- the day on which tablets should be taken. For example, methotrexate is most commonly given as a once-weekly dose (Box).[8] Fatal errors have occurred when methotrexate has been prescribed to be taken daily or when the incorrect strength of tablets has been prescribed.[9]

Wherever possible the quantity prescribed should be the quantity needed for one cycle (cancer chemotherapy) or one month (for example methotrexate for rheumatoid arthritis). Preferably, repeat prescriptions should not be issued as doses may change according to adverse effects and therapeutic response. If a repeat prescription is issued within the Pharmaceutical Benefits Scheme regulations, the patient should be directed to destroy any repeats or return them to the prescriber if treatment is changed or stopped.

Patients should always be advised on the action to take should they experience an adverse event – for example severe diarrhoea with capecitabine requires immediate cessation of therapy. Patients should be given the name of an accessible healthcare contact they can speak to regarding any concerns.

Box **Safe prescribing of weekly methotrexate** [8]

Provide the patient with verbal and written information on the intended schedule of therapy including the dose as a quantity of tablets and the frequency of dosing

Ensure handwritten prescriptions are complete and legible and include in full the form, strength, dose and directions

Nominate on the prescription the day on which the dose should be taken

Do not write 'as directed' on the prescription

Consider limiting the prescribed quantity of methotrexate to four weeks

Do not override warnings and flags for methotrexate in prescribing software

Keep the strength of tablet supplied to the patient consistent to avoid confusion for the patient over the number of tablets they need to take

Be aware of signs of methotrexate toxicity or intolerance, for example dry persistent cough, vomiting and diarrhoea

Patients should be advised to contact their doctor or pharmacist straight away if a dose is missed, or they develop an infection such as gastroenteritis or fever

If a patient is admitted to hospital, strike out the six days of the week when methotrexate is NOT required in the administration section of the inpatient medication chart

Dispensing and supplying oral cytotoxic treatment

The dispensing of oral cytotoxic therapy includes verification of the prescription for the patient and their condition, and appropriate supply in a safe and timely manner.[7] For cancer chemotherapy the pharmacist should have access to the treatment plan, the chemotherapy protocol and relevant patient parameters including height and weight and recent laboratory results.[10] The pharmacist should ensure that the relevant supportive medicine has been prescribed or is available to the patient.

Interactions between chemotherapy, other prescribed drugs, and over-the-counter and complementary medicines can cause changes in the efficacy and safety of oral chemotherapy.[11] For example, analgesic doses of aspirin and non-steroidal anti-inflammatory drugs can increase the toxicity of methotrexate when they are used with cancer therapy. Low-dose aspirin can be used with weekly methotrexate. The risk associated with lower doses of methotrexate used in rheumatoid arthritis therapy is much less.

Conversely cytotoxic chemotherapy can alter the effectiveness of other drugs. For example, capecitabine significantly reduces the metabolism of warfarin, increasing its anticoagulant effect. A complete medication history should be taken from the patient or carer before dispensing a prescription and potential interactions should be discussed.

If a dose administration aid (for example a Webster-pak) is required by the patient, then oral cytotoxics must be packed separately from the patient's non-cytotoxic medicines.

Medicine labelling

The labelling of oral cytotoxic therapy should clearly state the dose and the number of tablets to be taken. The label for weekly dosing for medicines such as methotrexate and vinorelbine should include the term 'once a week' and specify the day the dose should be taken. Cytotoxic chemotherapy can be carcinogenic, mutagenic and teratogenic. A warning sticker should be placed on all containers of cytotoxic chemotherapy tablets and capsules, in accordance with local health

and safety policy. An adhesive purple sticker with the wording 'cytotoxic, handle with care' is recommended. A warning label must be placed on administration aid packs that identify the contents as cytotoxic. Oral cytotoxic tablets and capsules should not be broken or crushed as this can increase the risk of exposure and alter the bioavailability of the medicine.

Information for the patient

Patient information is paramount to support the safe use of oral cytotoxic therapy. Patients should be given verbal and written information that includes dose instructions (when the medicine should be taken and if it is required to be taken before or after food), adverse effects and safe storage instructions.[7,12] Some oral cytotoxic medicines need to be stored securely in a refrigerator, for example chlorambucil and melphalan.

Patients should be advised that oral cytotoxic medicine should only be taken out of the dispensed packaging immediately before a dose. To minimise exposure of carers and family members to cytotoxic medicines, patients should be advised that self-administration is preferable. If administration by a carer is required then disposable gloves should be worn. Unused tablets must be returned to the local pharmacy or original supplier and not disposed of at home.

The intermittent, cyclical treatment that is characteristic of many cancer chemotherapy protocols is difficult for some patients to understand and they may misinterpret instructions. Medication guides, patient calendars and dose administration aids are often useful to help patients follow complex dose regimens, particularly those on multiple medicines. Adherence to oral therapy is important to maximise the benefits and reduce the risks of treatment. This should be discussed with the patient.

If appropriate, Consumer Medicine Information leaflets should be given to patients, however the context in which cytotoxic chemotherapy is used often limits their suitability. Patient information leaflets on many of the commonly used cancer chemotherapy protocols can be found on the eviQ Cancer Treatments Online website.[13] This website also provides information about how to safely take oral chemotherapy treatments at home.* The Australian Rheumatology Association provides patient information on drugs such as methotrexate and cyclophosphamide.[8]

Patients should be advised of the importance of notifying dentists, doctors and other healthcare professionals who may be involved in their care about their cytotoxic therapy.

Identifying and managing adverse effects

Cytotoxic chemotherapy causes many adverse effects such as nausea, vomiting, bone marrow suppression, stomatitis, diarrhoea, hand-foot syndrome, peripheral and central neurotoxicity, renal and liver dysfunction and hair loss. The effects require careful monitoring, and supportive therapies may be needed to minimise them. Antiemetics should be prescribed according to the emetogenic potential of the chemotherapy.[14] Nausea and vomiting can continue for several days after a dose of chemotherapy and the duration of antiemetic therapy should take this into consideration. Guidelines exist for prescribing antiemetics with cancer chemotherapy.[15,16]

Patient information is paramount to support the safe use of oral cytotoxic therapy

Blood counts need to be frequently checked with cytotoxic therapy. Patient monitoring, including laboratory tests and the parameters for initiating the next cycle of chemotherapy, should be clearly defined in the protocol or treatment plan. For example, a neutrophil count of greater than 1×10^9 is usually required for a cycle of cancer chemotherapy to proceed.

Particular care should be taken with patients when the cytotoxic therapy is taken continuously, for example cyclophosphamide or chlorambucil, as severe myelosuppression can develop. Cytotoxic chemotherapy can adversely affect liver and renal function and these should be monitored before each course of therapy.

Live vaccines are contraindicated in patients with impaired immune function which includes those receiving oral cytotoxic therapy. These vaccinations should usually be delayed until at least six months after the completion of any chemotherapy. Inactivated vaccines are generally safe, but patients may have a diminished immune response to the vaccine. The influenza vaccine should be administered before each influenza season and pneumococcal vaccine should be considered before starting therapy.

Recommendations

Despite the convenience that oral cytotoxic therapy offers, it carries the same risk of medication errors and adverse effects as parenteral therapy. Oral

* www.eviq.org.au/Protocol/tabid/66/categoryid/449/id/492/Patient+Information+-+Oral+Chemotherapy.aspx

cytotoxic medicines have a narrow therapeutic index and monitoring the patient for safety and efficacy is essential. Written and verbal communication with patients and carers is critical for the safe and appropriate use of cytotoxic therapy.

If a patient unknown to the prescriber, pharmacist or healthcare professional presents for oral cytotoxic therapy, the risk of continuing therapy should be balanced against the risk of stopping therapy until a full history and safety checks are done. In many cases delaying therapy for a short time while a full patient review is conducted and laboratory counts are obtained is safer than continuing therapy.

Dr Carrington served on advisory boards for Amgen and Merck Sharp & Dohme and has received honoraria from Roche and Merck Sharp & Dohme for educational presentations.

REFERENCES

1. The Institute for Safe Medication Practices. Lowdown on lomustine: we'd hate CeeNU make this mistake. ISMP Safety Alert; 2004 Jul 15. www.ismp.org/Newsletters/acutecare/articles/20040715.asp [cited 2013 Jan 7]
2. Holquist C, Phillips J. FDA Safety Page: fatal medication errors associated with Temodar. Drug Topics 2003;7:42. http://drugtopics.modernmedicine.com/drugtopics/DrugInformation/ArticleStandard/article/detail/110864 [cited 2013 Jan 7]
3. NHS National Patient Safety Agency UK. Rapid Response Report: risks of incorrect dosing of oral anti-cancer medicines. 2008 Jan 22:NPSA/2008/RRR001. www.nrls.npsa.nhs.uk/resources/?entryid45=59880 [cited 2013 Jan 7]
4. Weingart SN, Spencer J, Buia S, Duncombe D, Singh P, Gadkari M, et al. Medication safety of five oral chemotherapies: a proactive risk assessment. J Oncol Pract 2011;7:2-6.
5. Arnet I, Bernhardt V, Hersberger KE. Methotrexate intoxication: the Pharmaceutical Care process reveals a critical error. J Clin Pharm Ther 2012;37:242-4.
6. Department of Health Victoria. Quality use of medicines notice: Caution with oral chemotherapy for cancer. 2010. www.safetyandquality.gov.au/wp-content/uploads/2012/02/Oral-for-health-services-Victorian-Department-of-Health.pdf [cited 2013 Jan 8]
7. Carrington C, Stone L, Koczwara B, Searle C, Siderov J, Stevenson B, et al. The Clinical Oncological Society of Australia (COSA) guidelines for the safe prescribing, dispensing and administration of cancer chemotherapy. Asia Pac J Clin Oncol 2010;6:220-37.
8. Australian Rheumatology Association. Patient Information. 2012. www.rheumatology.org.au/community/PatientMedicineInformation.asp [cited 2013 Jan 7]
9. NHS National Patient Safety Agency UK. Improving compliance with oral methotrexate guidelines. 2006. NPSA/2006/13. www.nrls.npsa.nhs.uk/resources/healthcare-setting/community-hospital/?entryid45=59800&cord=ASC [cited 2013 Jan 7]
10. Carrington C, Gilbar P, Wintraeken J; The Society of Hospital Pharmacists of Australia Committee of Specialty Practice in Cancer Services. Standards of practice for the provision of pharmaceutical care of patients receiving oral chemotherapy for the treatment of cancer. J Pharm Pract Res 2007;37:149-52.
11. Goodin S. Oral chemotherapeutic agents: understanding mechanisms of action and drug interactions. Am J Health Syst Pharm 2007;64 Suppl 5:S15-24.
12. Viele CS. Managing oral chemotherapy: the healthcare practitioner's role. Am J Health Syst Pharm 2007;64 Suppl 5:S25-32.
13. Cancer Institute NSW. EviQ Cancer Treatments Online [website]. www.eviq.org.au [cited 2013 Jan 7]
14. Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson S, Rapoport BL, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity–an update. Support Care Cancer 2005;13:80-4.
15. Roila F, Herrstedt J, Gralla RJ, Tonato M. Prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: guideline update and results of the Perugia consensus conference. Support Care Cancer 2011;19 Suppl 1:S63-5.
16. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011;29:4189-98.

FURTHER READING

Risks associated with prescribing oral methotrexate [media release]. NPS MedicineWise. 2011 Dec 20. www.nps.org.au/media-centre/media-releases/repository/health-professionals-alert-to-the-risks-associated-with-oral-methotrexate [cited 2013 Jan 7]

Dental note

Safe use of oral cytotoxic drugs

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The increasing use of oral cytotoxic drugs for non-oncological diseases has resulted in an increased likelihood that dental patients will be taking them. The oral mucosa has a very high cell turnover rate and these drugs will invariably result in thinning of the mucosa, and often, concurrent salivary hypofunction. These patients are likely to require increased care and, if they have complex dental treatment needs, may require specialist management. Good communication with the treating doctors and appropriate referral where necessary will significantly help these patients.

ARTICLE

The competent prescriber: 12 core competencies for safe prescribing

SUMMARY

Prescribing errors remain a significant cause of patient harm. Safe prescribing is not just about writing a prescription, but involves many cognitive and decision-making steps.

A set of national prescribing competencies for all prescribers (including non-medical) is needed to guide education and training curricula, assessment and credentialing of individual practitioners.

We have identified 12 core competencies for safe prescribing which embody the four stages of the prescribing process – information gathering, clinical decision making, communication, and monitoring and review.

These core competencies, along with their learning objectives and assessment methods, provide a useful starting point for teaching safe and effective prescribing.

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Key words
prescribing, quality use of medicines

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Introduction

With the expansion of prescribing rights to non-medical prescribers, there is a need for an agreed set of national prescribing competencies for all prescribers.[1-3] NPS MedicineWise has recently launched a framework which can be used to guide education curricula, assessment, continuing professional development and credentialing of individual practitioners.[4] Our paper adds to this body of work.

How do we grow a good prescriber?

What makes a good prescriber? Prescribing is often thought of as just the act of writing a prescription, but it is a high-risk intervention such that the privilege to prescribe should require demonstration of competence.[5] It has been described as the process of deciding which medication to use and how to use it, while the prescription is the means by which these decisions are communicated.[6] Safe prescribing must include cognitive and decision-making steps before the prescription is generated.[6]

A good prescriber is a safe one. Unfortunately, a systematic review of junior doctors' prescribing found that the range of errors was wide (2–514 of 1000 items prescribed and 4–82% of patients or charts reviewed).[7]

Education is one of the most effective methods to prevent medication errors.[6,8,9] The World Health Organization Good Prescribing Guide was found to be useful in improving students' skills in multiple clinical settings.[9] It could serve as a foundation for a targeted prescribing curriculum, although further development in both the teaching and assessment of prescribing is warranted.[9] As an example, interactive case-based tutorials in therapeutic areas commonly associated with a high risk of patient harm were found to increase the ability of medical students to prescribe safely.[10]

Prescribing skills are usually learned during junior doctor training. For example, in general practice, registrars learn to prescribe mainly through their workplace experience.[11]

Prevention of medication errors can be improved through focused teaching and training. A set of principles have been developed to guide training of both undergraduates and postgraduates in the UK.[8] These include:

- protected time to update and reflect on prescribing, with feedback relevant to their area of practice
- supervision that allows discussion of problems, encouraging the seeking of advice
- feedback on identified prescribing errors in a blame-free learning environment.[8]

A good prescriber is a safe one

The four stages of prescribing

A four stage model of prescribing has been developed (Fig. 1).[12] This emphasises that prescribing is a staged process rather than a single event and is in line with UK prescribing competencies for new medical graduates.[8] These stages are:

1. Information gathering

The prescriber should have the skills to gather the relevant patient information such as medical history, including current symptoms, current and recently ceased or changed medications, allergies, adverse drug reactions and diagnoses.

2. Clinical decision making

Prescribers should be able to make clinical decisions. This includes making or reviewing a diagnosis, using pharmacological knowledge to select which medicine to use along with appropriate dosing for the individual patient. The prescriber should also consider non-drug treatments, and engage the patient in collaborative decision making to improve adherence and patient outcomes.[13]

The prescriber should be able to tailor their decision-making styles, for example directive or collaborative, and decide which is most appropriate for the patient at that point in time,[13] always valuing the patient's views[14].

3. Communication

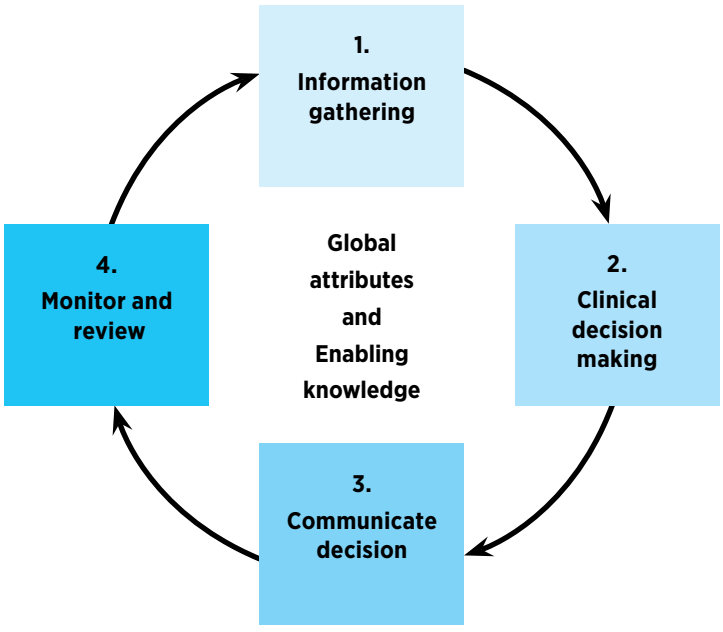
The prescriber should be able to convey the prescribing decision in a safe and effective manner to both the patient and to other health professionals involved. The prescription should be legible, unambiguous and without error-prone abbreviations for pharmacists to dispense and patients or nurses to administer. A management plan should be clear and contain triggers for referral or action. Both verbal and written communication skills are important. For example, the patient and their carer should be informed about why they have been prescribed a medication, how to use it and the expected duration of treatment. Monitoring requirements, potential adverse effects and contingency planning should also be discussed.

Electronic prescribing software with clinical decision support is now commonly used. Increasingly, electronic medicines management (including electronic inpatient medication charts) is being introduced. Along with the personally controlled electronic health record, these are powerful enablers of communication between prescribers, the healthcare team and the patient. Prescribers should become competent in using these tools.

4. Monitoring and review

The prescriber should be able to review the therapeutic or adverse effects of the treatment to inform dose adjustments or a change in treatment.

Fig. 1 **The four stage process of prescribing**



Adapted from reference 12

12 core prescribing competencies

For ease of use in curriculum design, assessment, training and development, 12 core competencies were defined (Table). These were aligned against competencies from other organisations[15-20] and two underpinning elements were added:

- enabling or foundational knowledge such as clinical pharmacology – without this the prescriber will be unable to move through the prescribing cycle. Pharmacological knowledge is essential to appropriate prescribing, and has been identified by junior doctors as an area to be strengthened in their training.[5]
- global attributes such as the ability and willingness to self-reflect on prescribing practice, seeking and acting on constructive feedback, as well as timely referral.

Teaching and assessing prescribing competencies

For each core competency, learning objectives (criteria for meeting that competency) and how these are assessed have been outlined. Fig. 2 illustrates this using core competency four – assessing adherence to current and past medications and risk factors for non-adherence. These may be a useful adjunct to the Australian Curriculum Framework for Junior Doctors which currently does not set out criteria for assessing junior doctors' performance.[20]

Methods

Adult learning principles should be used in teaching the core competencies, including self-evaluation and observation by peers or a mentor with structured advice, such as the agenda-led outcome-based feedback.[21] This method empowers the learner, reduces defensiveness, and allows an opportunity for change in behaviour. It identifies what help the learner

Table **12 core competencies for safe prescribing**

The four stages of prescribing *	12 core competencies
1. Information gathering • skill of gathering relevant information to inform selection of treatment	1. Take and/or review medical history 2. Take and/or review medication history and reconcile this with medical history 3. Undertake further physical examination/ investigations where appropriate 4. Assess adherence to current and past medication and risk factors for non-adherence
2. Decision making • collaborative decision making with the patient/carer; selection of treatment	5. Identify key health and/or medication related issues with the patient, including making or reviewing the diagnosis 6. Determine how well disease and symptoms are managed/controlled 7. Determine whether current symptoms are modifiable by symptomatic treatment or disease modifying treatment 8. Consider ideal therapy (drug and non-drug), taking into account actual and potential contraindications/concerns: drug–patient, drug–disease, drug–drug interactions 9. Select drug, form, route, dose, frequency, duration of treatment
3. Communicate decision • safely and effectively communicate treatment decisions to other health professionals and the patient/carer in both the ambulatory and the inpatient setting	10. Communicate prescribing decision in an ambulatory care setting 11. Communicate prescribing decision in an inpatient setting
4. Monitor and review • review therapeutic and adverse impact of treatment	12. Review control of symptoms and signs, adherence, patient's outcomes

* The four stages are underpinned by two extra elements – enabling knowledge, particularly clinical pharmacology, and global attributes such as self-reflection on prescribing

wants and enables them to achieve learning goals by encouraging self-assessment.

The skills, attitudes and behaviours needed for prescribing could be shown and learned through simulated scenarios. Assessment should comprise a variety of methods so as to include the most appropriate format for any particular criterion.[22] For example, to best evaluate whether a prescriber has acquired skills in detecting non-adherent behaviour (core competency four), the prescriber should be directly observed interacting with a patient.

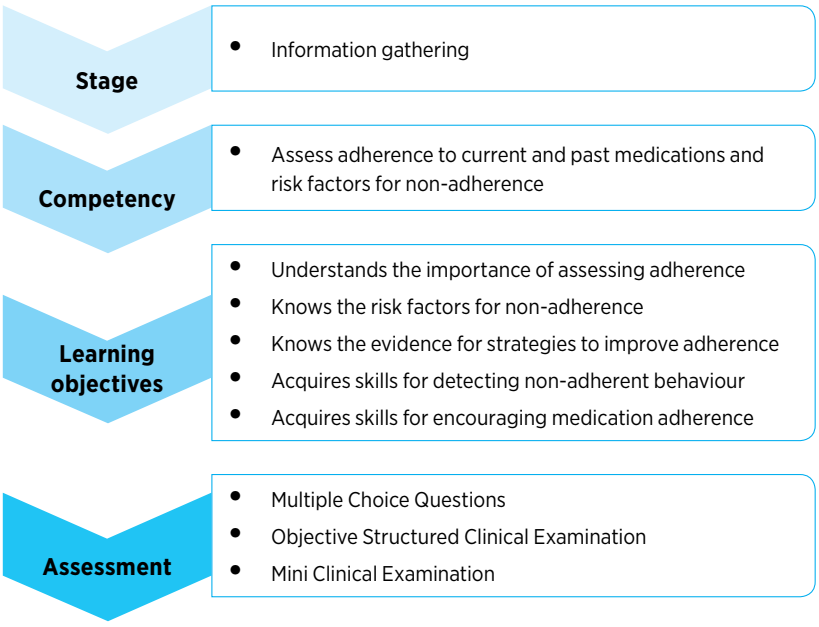
This is in line with Miller's Pyramid[23] which describes four levels for assessing clinical skills, competence and performance:

1. knows
2. knows how
3. shows
4. does.

Achievement of level four is assessed through direct observation. To demonstrate prescribing competence, assessing at 'shows' and 'does' levels becomes important although it is more resource intensive and challenging to coordinate. Currently, direct observation of procedural skill is required in order to be deemed competent in surgical procedures. This should equally apply to prescribing.

Multiple source feedback such as peer assessment or 360° feedback can be used to ascertain if

Fig. 2 **An illustration of core competency 4 in the information gathering stage and its accompanying competency, learning objectives and assessment methods**



communication is clear to other clinicians and to patients and carers. Other means of assessing prescribing competency could include clinical audits of prescribing. These may be structured self audits such as those developed by NPS MedicineWise* or targeted clinical audits coordinated within a healthcare facility. Timely feedback to prescribers to close the loop is essential.

A useful method for evaluating nurse prescribing combines practice-based observations with a structured competency checklist, analysis of written prescriptions and documentation of the prescribing episode in the medical record.[24]

Registrars have expressed difficulty in judging the quality of their own prescribing.[11] The 12 core prescribing competencies and their accompanying criteria and assessments could serve as a formative tool for giving explicit feedback about the process and outcome of prescribing decisions. The competencies can also be used as a summative tool.

Credentialing as competent to prescribe

It has been recommended that qualification as a doctor, which includes a licence to prescribe, be contingent on passing an undergraduate prescribing examination. It has been suggested that clinicians should be reassessed to retain this privilege.[25]

Conclusion

A perennial tension exists between higher education providers (for example medical schools) and employers (for example health facilities) as to where responsibility lies in producing a graduate who is 'fit for purpose'. When a prescribing error occurs during the early weeks of internship, which party has failed? Closer collaboration between teaching and training graduates is clearly warranted. This could be facilitated by adopting a set of national prescribing competencies and agreeing to adopt set criteria and a framework for assessment. The benefits of standardised prescribing competencies may not otherwise be realised. The 12 core competencies and their accompanying methods of assessment provide a useful starting point for this work, although feasibility of the proposed assessment methods needs broader discussion. ◁

Adjunct Associate Professor Coombes is a member of the Editorial Executive Committee of Australian Prescriber.

* www.nps.org.au/health-professionals/professional-development/clinical-audits-for-gps

REFERENCES

1. Nissen L, Kyle G. Non-medical prescribing in Australia [editorial]. Aust Prescr 2010;33:166-7.
2. Morris S, Coombes I. The right to prescribe: towards core prescribing competencies for all prescribers [editorial]. Aust Prescr 2011;34:126-7.
3. National Prescribing Centre. A single competency framework for all prescribers. National Institute for Health and Clinical Excellence. 2012.
4. Prescribing Competencies Framework. NPS MedicineWise. 2012. http://www.nps.org.au/health-professionals/professional-development/prescribing-competencies-framework [cited 2013 Jan 7]
5. Pillans P. How prepared are medical graduates to begin prescribing? Intern Med J 2009;39:425-7.
6. Aronson JK. Medication errors: EMERGing solutions. Br J Clin Pharmacol 2009;67:589-91.
7. Ross S, Bond C, Rothnie H, Thomas S, Macleod MJ. What is the scale of prescribing errors committed by junior doctors? A systematic review. Br J Clin Pharmacol 2009;67:629-40.
8. Likic R, Maxwell SR. Prevention of medication errors: Teaching and training. Br J Clin Pharmacol 2009;67:656-61.
9. Ross S, Loke YK. Do educational interventions improve prescribing by medical students and junior doctors? A systematic review. Br J Clin Pharmacol 2009;67:662-70.
10. Coombes I, Mitchell C, Stowasser D. Safe medication practice tutorials: a practical approach to preparing prescribers. Clin Teacher 2007;4:128-34.
11. Ajjawi R, Thistlethwaite J, Aslani P, Cooling N. What are the perceived learning needs of Australian general practice registrars for quality prescribing? BMC Med Educ 2010;10:92.
12. Coombes I, Reid C, McDougall D, Stowasser D, Duiguid M, Mitchell C. Pilot of a national inpatient medication chart in Australia: improving prescribing safety and enabling prescribing training. Br J Clin Pharmacol 2011;72:338-49.
13. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ 2009;339:b2803.
14. Bond C, editor. Concordance: a partnership in medicine-taking. London: Pharmaceutical Press; 2004.
15. Outcomes of the Medical Schools Council Safe Prescribing Working Group. Medical Schools Council, UK. 2008. www.medschools.ac.uk/Publications/Pages/Safe-Prescribing-Working-Group-Outcomes.aspx [cited 2013 Jan 7]
16. National Prescribing Centre. Maintaining competency in prescribing: an outline framework to help nurse prescribers. 1st ed. National Institute for Health and Clinical Excellence. 2001. www.npc.nhs.uk/non_medical/resources/maint_comp_prescribing_nurs.pdf [cited 2013 Jan 7]
17. Frank JR, editor. The CanMEDS 2005 Physician Competency Framework. The Royal College of Physicians and Surgeons of Canada. 2005.
18. Accreditation Council for Graduate Medical Education (USA). Competency Based Residency Education. 2006. www.acgme.org/acgmeweb/Portals/0/PFAssets/ProgramResources/Common_Program_Requirements_07012011%5B1%5D.pdf [cited 2013 Jan 7]
19. de Vries TPGM, Henning RH, Hogerzeil HV, Fresle DA. Guide to Good Prescribing: a practical manual. Geneva: World Health Organization Action Programme on Essential Drugs; 1994. http://apps.who.int/medicinedocs/en/d/Jwhozip23e [cited 2013 Jan 7]
20. Australian Curriculum Framework for Junior Doctors. Version 2.2. Confederation of Postgraduate Medical Education Councils. 2009.
21. Kurtz S, Silverman J, Draper J. Teaching and learning communication skills in medicine. 2nd ed. Oxford: Radcliffe Publishing; 2005.
22. Holmboe ES, Hawkins RE. Methods for evaluating the clinical competence of residents in internal medicine: a review. Ann Intern Med 1998;129:42-8.
23. Miller GE. The assessment of clinical skills/competence/performance. Acad Med 1990;65(9 Suppl):s63-7.
24. Latter S, Maben J, Myall M, Young A, Baileff A. Evaluating prescribing competencies and standards used in nurse independent prescribers' prescribing consultations: an observation study of practice in England. J Res Nurs 2007;12:7-26.
25. Aronson JK, Henderson G, Webb DJ, Rawlins MD. A prescription for better prescribing [editorial]. BMJ 2006;333:459-60.

FEATURE

Medicinal mishap

Flecainide and neutropenia

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Case

A 73-year-old woman was admitted to hospital for investigation following a short episode of slurred speech which was diagnosed as a transient ischaemic attack. She had a history of paroxysmal atrial fibrillation, transient ischaemic attacks, essential hypertension, duodenal ulcer, chronic hepatitis B infection and acoustic neuroma.

Her drug history found that she had been switched from metoprolol to flecainide 50 mg twice a day for control of her atrial fibrillation three months previously. The only other drug she had been taking was omeprazole 20 mg twice a day for two years.

An incidental finding on admission was a white blood cell count of 2.5 x 10^9/L, with a neutrophil count of 0.61 x 10^9/L. Reactive lymphocytes were present. The remaining white cell differential was within normal ranges. Haemoglobin was normal, with a slightly raised mean cell volume. Platelet count was reduced at 127 x 10^9/L.

Liver function tests were mildly abnormal, consistent with chronic hepatitis B infection. Renal function was normal for age and testing for autoimmune and rheumatoid disorders, HIV and haematological malignancy was negative. C-reactive protein was 15 mg/L and erythrocyte sedimentation rate was 19 mm/hour.

On day two of admission, the neutrophil count dropped to 0.28 x 10^9/L. Flecainide was ceased on the same day. Five days after stopping flecainide, the neutrophil count had risen to 1.59 x 10^9/L. Omeprazole was continued throughout and metoprolol reinstated for rate control of her atrial fibrillation.

Comment

Flecainide is a class 1c antiarrhythmic drug indicated for use in supraventricular arrhythmias in patients without structural heart disease. It is not recommended for use in chronic atrial fibrillation.

Agranulocytosis is a rare but serious complication of antiarrhythmic drugs. It has previously been associated with procainamide, quinidine and flecainide. The mechanism by which agranulocytosis develops with flecainide is not clearly understood, however a putative mechanism involves the development of flecainide-specific IgG antibodies.[1,2]

This is the first case of flecainide-induced neutropenia reported to the Therapeutic Goods Administration in which no other drugs were suspected to have contributed.[3] There have been 32 cases reported to the Food and Drug Administration in the USA, with three-quarters of cases occurring within six months of starting flecainide.[4]

In this case the neutropenia could not be attributed to any other drug, concurrent disease or infection. Additionally, there was a plausible time relationship between starting flecainide and developing a neutropenia which resolved after the drug was stopped.

Conclusion

There was a probable causal association between flecainide and neutropenia. This is a rare adverse reaction associated with some antiarrhythmic drugs and this may be the first such report in Australia.

REFERENCES

1. Samlowski WE, Frame RN, Logue GL. Flecanide-induced immune neutropenia. Documentation of a hapten-mediated mechanism of cell destruction. Arch Intern Med 1987;147:383-4.
2. Starkebaum G, Kenyon CM, Simrell CR, Creamer JI, Rubin RL. Procainamide-induced agranulocytosis differs serologically and clinically from procainamide-induced lupus. Clin Immunol Immunopathol 1996;78:112-9.
3. Database of Adverse Event Notifications [database]. Canberra: Australian Government Department of Health and Ageing, Therapeutic Goods Administration. 2012. www.tga.gov.au/DAEN/daen-report.aspx [cited 2013 Jan 7]
4. Could flecainide acetate cause neutropenia, in real world? eHealthMe - Real world drug outcomes. 2012. www.ehealthme.com/ds/flecainide+acetate/neutropenia [cited 2013 Jan 7]

ARTICLE

Safe and effective use of lithium

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bipolar disorder, mood stabiliser, tolerability

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SUMMARY

Lithium has proven efficacy in the treatment of bipolar disorder, both for acute mania and long-term mood stabilisation and prophylaxis.

It is also useful in combating treatment-resistant depression.

Compared to other mood stabilisers, lithium has a favourable efficacy–tolerability balance.

Lithium is underused due to active marketing of alternatives and concerns regarding adverse effects, tolerability, and the perception that regular monitoring is difficult.

Introduction

Lithium has been available for over sixty years for bipolar disorder. A large empirical evidence base has ensured it remains a viable treatment option, even in the absence of sponsorship and promotion.[1-3]

Lithium has unique properties both as an antisuicidal and neuroprotective drug and, if used wisely, is relatively well tolerated and not complex to administer. Despite this, its role as a mood stabiliser in practice has been limited because of concerns regarding tolerability and long-term risks, and the perception that regular and reliable monitoring of plasma concentrations is difficult.

Efficacy in bipolar disorder

Lithium is particularly effective in patients with recurrent bipolar I disorder in which episodes of depression and mania are punctuated by periods of remission (euthymia). Complex forms of bipolar disorder such as bipolar II disorder, mixed states, and rapid cycling are common, but respond less well to lithium (Table 1).

In recent years the reported response to lithium in bipolar disorder has diminished. This is partly because studies investigating new treatments, in which lithium has often served as a comparator, have increasingly used heterogeneous bipolar populations.[4] The patients usually have mixtures of bipolar disorder 'subtypes' from bipolar I disorder to major depression. Studies in first world countries often enrol individuals who have been refractory to pharmacotherapy, so not surprisingly the efficacy of lithium appears lower than expected.

A recent real-world study comparing lithium and valproate alone and in combination reaffirmed lithium as an effective first-line drug for maintenance therapy and perhaps the best drug for prophylaxis.[5] Recent guidelines state that in addition to its clear prophylactic properties, lithium is also efficacious in the acute phases of bipolar disorder (Table 1).[6]

Mania

Robust randomised controlled data from trials indicate that lithium is effective in treating acute mania. However, its relatively slow onset of action (6–10 days) means it is used in combination with short-term antipsychotics and benzodiazepines.[1]

Depression

The evidence for lithium monotherapy in the treatment of bipolar depression is not as impressive as that for mania, partly because it can take 6–8 weeks to take effect. Recent clinical trials suggest that lithium is more effective than placebo and therefore it remains an important option for treating bipolar depression.[7]

Maintenance and prophylaxis

The efficacy of lithium in prophylaxis has been robustly demonstrated by the BALANCE study.[5] With adequate adherence, long-term lithium successfully reduces suicidal ideation.[1] Consistency of treatment is therefore important and commencing maintenance therapy early provides the best possibility of improved long-term outcomes.[3] Furthermore, long-term therapy may confer neuroprotection by enhancing the viability of cells as well as preventing apoptosis.

Rapid cycling bipolar disorder and mixed states

Clinically, rapid cycling bipolar disorder and mixed states can often be difficult to differentiate[1] and in practice lithium is relatively less effective in achieving remission in both of these subtypes compared to bipolar I disorder. However, it does reduce symptom severity and can therefore be used combined with other psychotropic medications, especially when wanting to reduce the risk of suicide and achieve prophylaxis.

Starting lithium therapy

Lithium is available in a variety of formulations. The sustained slow-release formulation will have a lower

Table 1 **Lithium in mood disorders**

Bipolar disorder	
Acute mania	Lithium monotherapy is a first-line option Antimanic action can take 6–10 days In practice lithium is often used in combination with neuroleptics and/or benzodiazepines to achieve a more rapid effect
Acute depression	Lithium monotherapy is less effective in treating acute depression than it is in treating mania Effect of antidepressant action can take 6–8 weeks Often used to augment mood stabiliser or antidepressant therapy
Maintenance/prophylaxis	Lithium is superior to placebo and most anticonvulsants and neuroleptics used in the treatment of bipolar disorder Outcome is better if therapy is initiated early
Rapid cycling/mixed states	Lithium is shown to decrease symptom severity and reduce morbidity, but is less likely to achieve remission of symptoms and recovery
Major depression	
Acute	Lithium monotherapy is superior to placebo but it is rarely used, particularly in acute settings Greater efficacy for patients with a family history of bipolar disorder
Chronic	Often used as an augmentation strategy Effective in combination with all antidepressants and can be prescribed adjunctively with all treatment modalities

peak plasma concentration which may be better tolerated by some patients. After oral administration lithium is absorbed in the gut and excreted wholly via the kidneys. It has very few interactions relating to hepatic metabolism. Steady-state lithium concentrations can usually be achieved after 4–5 days of daily administration. Lithium has a relatively narrow therapeutic index so it is important to maintain lithium plasma concentrations within a specific range for each individual to achieve a balance between efficacy and adverse effects.

To minimise adverse effects when starting lithium de novo it should be administered in small divided doses then titrated gradually to achieve plasma concentrations of 0.6–0.8 mmol/L, while monitoring for these effects. Concentrations of up to 0.8–1.0 mmol/L may be needed for lithium-naïve patients and for treating acute recurrence of mania. Recent long-term studies suggest that even relatively low concentrations (0.6–0.8 mmol/L) confer reasonable prophylaxis, and are better tolerated.

Maintenance and prophylaxis therapy

The primary aim of prophylaxis is to prevent the recurrence of symptoms while minimising adverse effects and maintaining compliance. Lithium can be given as a once-daily dose for maintenance therapy. Most importantly, plasma lithium concentrations should be optimised to the symptom profile of the individual. Patients more prone to developing depressive episodes may benefit from concentrations of 0.4–0.8 mmol/L, whereas those more likely to become manic may require concentrations of 0.6–1.0 mmol/L long term.

Short-term adverse effects

Tremor, general fatigue, diarrhoea, thirst, polyuria, nausea, headache and vomiting are common initially, but are usually transient (1–2 days) and dose dependent. Most of these adverse effects are associated with rapid changes in plasma lithium concentrations and therefore should be anticipated whenever the dose of lithium is altered, and especially when it is increased.[8] If adverse effects persist for weeks or are particularly troublesome, lithium should be decreased or stopped. In practice this is rarely necessary and lithium can usually be reintroduced while titrating the dose carefully.

Long-term adverse effects

There are several adverse effects associated with long-term use of lithium and regular patient monitoring is required (Table 2).

Kidneys

Lithium affects the concentrating ability of the kidney, leading to polyuria and secondary thirst, but it is controversial whether lithium causes irreversible kidney damage. Approximately 10% of patients on lithium are prone to developing diabetes insipidus.[9] It is this renal insufficiency which is often thought to contribute to end-stage renal failure. Patients with renal impairment may remain on lithium treatments with appropriate dosage adjustments.

Thyroid

Lithium also affects thyroid function reducing the availability of thyroxine. The incidence of hypothyroidism is six-fold higher in patients on lithium as compared to the general population. Hypothyroidism in turn increases the likelihood of developing clinical depression.[8] Patients on lithium should therefore be routinely assessed for hypothyroidism and treated with thyroxine replacement if indicated.[8] It needs to be stressed however that hypothyroidism is not a contraindication for therapy.

Parathyroid

Parathyroid function can also be compromised by lithium. Patients on lithium are therefore prone to develop hypercalcaemia secondary to elevated parathyroid concentrations. Hyperparathyroidism that produces significant hypercalcaemia is a possible contraindication for continuing lithium so there is a need to monitor plasma calcium concentrations.[10]

Weight gain

Modest weight gain of 1–2 kg is common (5%) in patients on long-term lithium therapy. The trajectory of weight gain is steep at the beginning but soon plateaus. Diet, exercise and lifestyle advice are essential when patients start treatment.

Teratogenic effects

It appears that the risk of teratogenic effects from lithium has been exaggerated in the past.[10] However, there is a small risk and lithium is best avoided during pregnancy. Management during pregnancy should be collaborative and requires careful informed consideration of the risks.

Toxicity and its management

In acute lithium intoxication, the increase in plasma concentrations (>2 mmol/L) can be potentially lethal. Once renal excretion reaches its maximum, lithium accumulates rapidly and symptoms worsen. However, high plasma concentrations may cause relatively mild symptoms, and in these instances individuals often recover without permanent neurological damage. This occurs because lithium can take up to 24 hours to cross the blood–brain barrier, and brain concentrations usually peak eight hours after oral administration.

With lifelong treatment, lithium can gradually accumulate within the brain and lead to chronic neural toxicity because it has a longer half-life in the brain than in plasma. Symptoms such as lethargy, drowsiness, muscle weakness and hand tremor are indicative of neural toxicity and can manifest even at therapeutic concentrations of lithium. Toxicity from chronic lithium use is also subject to increases in dose and individual factors such as diminished renal function and ageing which may result in increased plasma concentrations.

It is therefore essential to monitor patients for symptoms of toxicity and assess plasma lithium concentrations every 3–6 months. If toxicity occurs, treatment should be stopped and prompt action taken to prevent serious damage.

Monitoring lithium

While it is generally recommended that plasma lithium concentrations may be monitored every 3–6 months,[11] current evidence suggests that unless otherwise indicated, annual monitoring may be sufficient (Table 2).

Table 2 **Recommendations for monitoring patients on lithium**

Parameter	Investigation	When to monitor
Lithium	Plasma lithium concentrations *	Monitor closely for first few days and aim to achieve concentrations within the therapeutic range Monitor every 3–6 months for long-term lithium use
Renal function	Urea and creatinine	Baseline then at 6 months
	Electrolytes	Baseline then annually
Thyroid function	Thyroid stimulating hormone concentrations	Baseline then at 6 months Annually for long-term lithium use
Parathyroid function	Calcium concentrations	Baseline then annually
Weight	Waist circumference, body mass index	Baseline then annually

Adapted from guidelines from the International Society for Bipolar Disorders.[11] More frequent investigation may be required if clinically indicated or a change in mood state is observed.

* In the event of acute toxicity (>2 mmol/L), lithium should be ceased immediately and haemodialysis can be used to reduce lithium in the blood

Adherence

Adverse effects are the most commonly cited reason for poor adherence. Of these, weight gain is the most distressing.[8] Not surprisingly, individuals who report multiple adverse effects are less likely to be adherent, and additional factors such as stigma and acceptance of the illness are important to bear in mind.[12]

The need to take medication when symptom-free is a key concern. This viewpoint often reflects a degree of denial by the patient because they are feeling better. This is more evident in younger individuals, those who have been recently diagnosed, and those taking lithium long-term. Patients who are not in a strong doctor–patient relationship and those who are less informed about the disorder and its treatment are generally less adherent.

Enhancing adherence requires a multifaceted approach involving education and monitoring of the patient. Close monitoring of patients improves adherence in two ways. First, it allows tailoring of the therapeutic dose to suit the individual, so that therapeutic benefit is optimised and the likelihood of adverse effects is minimised. Second, regular monitoring increases contact and therefore patients are likely to receive more frequent supervision and better education concerning their illness and its management.

Other strategies include educating family and friends to recognise the early signs of relapse and using a suitable means to manage stressors. Caregiver support increases adherence.[13] Encouraging patients to make a firm commitment to treatment before it starts, and coupling pharmacotherapy with psychotherapy, have also been shown to improve patient outcomes.[8]

Conclusion

Lithium can be used as monotherapy or in combination with other medications for the treatment of bipolar disorder. It is most efficacious in maintenance and prophylaxis and is widely used as a mood stabiliser, and has efficacy in both poles of the disorder. It is important to monitor both response and adverse effects and to regularly measure the plasma concentrations of lithium. This ensures adequacy of treatment and enhances compliance. If used wisely, lithium is relatively well tolerated and not complex to administer. It remains one of a handful of potentially life-changing treatments in psychiatry. ⋖

Lithium is relatively well tolerated and not complex to administer

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REFERENCES

1. Malhi GS, Adams D, Berk M. Is lithium in a class of its own? A brief profile of its clinical use. Aust N Z J Psychiatry 2009;43:1093-104.
2. Young AH, Hammond JM. Lithium in mood disorders: increasing evidence base, declining use? Br J Psychiatry 2007;191:474-6.
3. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004;161:217-22.
4. Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. Br J Psychiatry 2010:196;266-73.
5. Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010;375:385-95.
6. Malhi GS, Adams D, Lampe L, Paton M, O'Connor N, Newton LA, et al. Clinical practice recommendations for bipolar disorder. Acta Psychiatr Scand Suppl 2009:27-46.
7. Fountoulakis KN. An update of evidence-based treatment of bipolar depression: where do we stand? Curr Opin Psychiatry 2010;23:19-24.
8. Yatham L, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 2009;11:225-55.
9. Bendz H, Aurell M. Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf 1999;21:449-56.
10. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet 2012;379:721-8.
11. Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 2009;11:559-95.
12. Berk L, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C, et al. Enhancing medication adherence in patients with bipolar disorder. Hum Psychopharmacol 2010;25:1-16.
13. Berk L, Jorm AF, Kelly CM, Dodd S, Berk M. Development of guidelines for caregivers of people with bipolar disorder: a Delphi expert consensus study. Bipolar Disord 2011;13:556-70.

FURTHER READING

Malhi GS, Tanious M, Gershon S. The lithiumeter: a measured approach. Bipolar Disord 2011;13:219-26.

ARTICLE

ECT in the 21st century: ultrabrief pulse stimulation

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SUMMARY

Ultrabrief pulse stimulation is a new advance in electroconvulsive therapy and results in more focal stimulation. An ultrabrief pulse given in the right unilateral position retains the high efficacy of standard electroconvulsive therapy for depression.

Cognitive adverse effects are greatly reduced. Studies of ultrabrief electroconvulsive therapy found that cognition was either unchanged or even improved, after the course of treatment.

The efficacy and cognitive adverse effects of ultrabrief electroconvulsive therapy in disorders other than depression need further examination.

Introduction

Electroconvulsive therapy (ECT) involves the therapeutic induction of a seizure while the patient is under general anaesthesia. It is mainly used to treat severe depression, although there is evidence to support its use in some other psychiatric disorders.[1,2]

A recent large multicentre trial showed that approximately a third of depressed patients failed to attain remission, even after trying four antidepressant drugs.[3] Many of these patients will require treatment with ECT. This is effective in 50–60% of the patients with drug-resistant depression. ECT has also been shown to have superior efficacy to antidepressants in head-to-head comparisons.[1] A study showed improvement in quality of life and function immediately after ECT treatment in 87% of patients and in 78% six months later.[4]

There are concerns over the risk of cognitive adverse effects of ECT. A recent systematic review and meta-analysis found that cognitive impairment tends to be transient and often resolves in the week after ECT.[5] Nevertheless, some patients experience significant and more persistent impairment. This has constrained the use of this otherwise highly effective treatment.

Research in typical clinical settings showed that while efficacy was high and did not differ significantly between treatment centres,[6] cognitive adverse effects varied from minimal to severe, depending on the treatment approach used.[7] This has led to research into modifications that could minimise the cognitive adverse effects of ECT.

Ultrabrief pulse width stimulation

A major advance which is currently emerging into clinical practice throughout Australia is ultrabrief pulse width ECT. In this approach, pulses in the electrical stimulus are shortened from about 1 millisecond to 0.3 millisecond. This is close to the ideal pulse width for activating neurons (0.1–0.2 millisecond) so seizures are induced at lower energy levels. The electrical dose used is 30–50% of that used in standard ECT. Computer modelling suggests that a smaller area of brain tissue is directly activated when the pulse width of the ECT is reduced – that is, the stimulation becomes more focal.[8] Although the pulse is brief an anaesthetic is still required.

Evidence (Table)

A double-blind, randomised trial found that for right unilateral ECT (where the stimulus was mainly applied to the right hemisphere, which for most patients is the non-dominant hemisphere) the efficacy of ultrabrief and standard pulse width treatment was similar (with 77% and 73% of patients attaining remission). Cognitive outcomes were far superior in the ultrabrief group.[9] Detailed neuropsychological testing done in the week after the end of ECT found no impairment on any test, compared to pre-ECT baselines, in the ultrabrief group, while some impairment was found with standard ECT. For bilateral ECT (where the stimulus is applied equally to both cerebral hemispheres), the ultrabrief stimulation was not so effective, for reasons that are not well understood.

Another trial confirmed good efficacy with ultrabrief unilateral ECT. There was no cognitive impairment, tested at one and six weeks after the end of ECT, compared to pre-ECT baselines.[10,11] On some measures, patients actually showed improvement in cognitive function after ECT, probably reflecting the significant improvement in depression.

A Sydney hospital compared ultrabrief and standard pulse width right unilateral ECT in the largest sample reported to date (96 patients).[12,13] This was not a randomised controlled trial but enrolled a range of patients typically prescribed ECT in clinical services. Efficacy outcomes were good for ultrabrief ECT.

However the results suggested that, compared to standard ECT, a few more treatments may be required for full therapeutic response. This may mean a longer hospital stay, depending on whether patients can receive the later treatments of an ECT course as outpatients. The speed of response to ultrabrief ECT may be slower, but this requires further exploration. Cognitive outcomes after ECT were substantially superior in the ultrabrief group.

The clinical trials are further supported by a number of subsequent reports about ultrabrief pulse width ECT.[14] No safety concerns specific to ultrabrief ECT have been reported, and given the substantial advantage in cognitive outcomes, it may overall be considered a safer treatment than standard ECT. Not all patients will respond to ultrabrief right unilateral ECT. Some patients may require switching to standard pulse width ECT.

Future developments

The studies which have reported on the use of ultrabrief pulse width ECT were almost exclusively in depressed patients.[14] It is likely that the dramatic reduction in cognitive adverse effects with this treatment approach will also be seen in other psychiatric disorders, such as mania and schizophrenia. This will need to be confirmed in future studies. At present, ultrabrief pulse width ECT is gradually emerging into clinical practice, but is not yet offered in the majority of Australian hospitals. ◁

Professor Loo is the chief investigator for an ongoing clinical trial of ultrabrief pulse width ECT at the Wesley Hospital in Sydney, funded by the National Health and Medical Research Council.

Q:

SELF-TEST QUESTIONS

True or false?

3. No anaesthetic is needed for ultrabrief pulse width ECT.
4. Depressed patients respond more rapidly to ultrabrief ECT than to standard ECT.

Answers on page 35

Table **Comparison of ultrabrief and standard electroconvulsive therapy**

Design	Number of patients	Therapeutic outcomes % responders (mean number of treatments required)				Cognitive outcomes
		Ultrabrief right unilateral ECT	Standard right unilateral ECT	Ultrabrief bilateral ECT	Standard bilateral ECT	
Retrospective comparison, age and gender matched[12]	60	57% (after 11.8 treatments)	50% (after 8.8 treatments)			Not assessed
Open label, non-randomised trial[13]	96	74 patients: 43% (after 10.3 treatments)	50% (after 7.6 treatments)			Ultrabrief right unilateral ECT had superior outcomes in frontal and memory (anterograde and retrograde) function
Double-blind, randomised, controlled trial[9]	90	77% (after 8.7 treatments)	73% (after 8.5 treatments)	48% (after 8.9 treatments)	70% (after 8.2 treatments)	Ultrabrief groups had superior outcomes in orientation, attention and concentration, memory (anterograde and retrograde) and frontal function
Double-blind, randomised, controlled trial[10,11]	64	78% (after 7.8 treatments)		78% (after 10.1 treatments)		Ultrabrief groups showed improved functioning in memory, attention, frontal functioning and global cognitive functioning after ECT, compared to pre-ECT performance

REFERENCES

1. UK ECT Review Group. Electroconvulsive therapy: systematic review and meta-analysis of efficacy and safety in depressive disorders. Lancet 2003;361:799-808.
2. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev 2005;2:CD000076.
3. Rush AJ. Limitations in efficacy of antidepressant monotherapy. J Clin Psychiatry 2007;68 Suppl 10:8-10.
4. McCall WW, Prudic J, Olfson M, Sackeim H. Health-related quality of life following ECT in a large community sample. J Affect Disord 2006;90:269-74.
5. Semkovska M, Keane D, Babalola O, McLoughlin DM. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. J Psychiatr Res 2011;45:770-80.
6. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. Biol Psychiatry 2004;55:301-12.
7. Sackeim HA, Prudic J, Devanand D, Fuller R, Keilp J, Lavori PW, et al. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology 2007;32:244-54.
8. Bai S, Loo C, Al Abed A, Dokos S. A computational model of direct brain excitation induced by electroconvulsive therapy: comparison among three conventional electrode placements. Brain Stimul 2011;5:408-21.
9. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 2008;1:71-83.
10. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Randomized comparison of ultra-brief and unilateral electroconvulsive therapy for major depression: clinical efficacy. J Affect Disord 2009;116:106-12.
11. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects. J Affect Disord 2010;122:60-7.
12. Loo C, Sheehan P, Pigot M, Lyndon W. A report on mood and cognitive outcomes with right unilateral ultrabrief pulsewidth (0.3 ms) ECT and retrospective comparison with standard pulsewidth right unilateral ECT. J Affect Disord 2007;103:277-81.
13. Loo C, Sainsbury K, Sheehan P, Lyndon B. A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. Int J Neuropsychopharmacology 2008;11:883-90.
14. Loo C, Katalinic N, Martin D, Schweitzer I. A review of ultrabrief pulse width electroconvulsive therapy. Ther Adv Chronic Dis 2012;3:69-83.

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Medicines Safety Update

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In this issue

Progressive multifocal leukoencephalopathy – a rare but serious disease

Immunomodulatory medicines have emerged as a class of medicines associated with the development of progressive multifocal leukoencephalopathy.

Awareness of risk factors and early recognition of symptoms is important as early diagnosis is likely to improve the prognosis.[1]

What is PML?

Progressive multifocal leukoencephalopathy (PML) is a rare, but often fatal, demyelinating disease of the central nervous system. PML is caused by lytic infection of oligodendrocytes and astrocytes resulting in multiple areas of demyelination in the central nervous system.

PML lesions are typically asymmetrical demyelinated plaque areas with irregular borders, surrounded by macrophages and irregular astrocytes with large, multiple nuclei.[2] On magnetic resonance imaging (MRI), the lesions usually do not show oedema, mass effect or gadolinium enhancement, which are common in multiple sclerosis.[2]

Patients with PML can have a variety of symptoms including muscle weakness, sensory deficit, cognitive dysfunction, language impairment and/or coordination and gait difficulties.[3]

What causes PML?

PML is caused by a human polyomavirus, the JC virus. The virus was named after the patient from whom it was initially cultivated, John Cunningham. Approximately 50% of the world's population are infected with the virus by the time they reach age 20, although most remain asymptomatic.[4] After initial virus infection, the virus remains quiescent in the kidneys, bone marrow and lymphoid tissue.[3]

In immunocompromised individuals the quiescent virus can reactivate, enter the bloodstream and then gain entry to the central nervous system where it infects oligodendrocytes and astrocytes. Infection of these cells leads to cell death, and the resulting demyelination produces the neurological signs and symptoms of PML.[5]

Viruses isolated from the brains of individuals with PML have a genomic rearrangement in the regulatory region that is not found in the strains responsible for initial infection.[4,5]

What are the risk factors?

Patients who are immunosuppressed or have a malfunction of the immune system are at higher risk of developing PML. Cell-mediated immunity disorders are the major immunological disorders that predispose individuals to the development of PML.[4]

PML cases have been reported in patients with HIV, lymphoproliferative disorders, malignancies, patients on immunosuppressive therapy after solid organ transplantation and in rheumatic diseases such as systemic lupus erythematosus.[6,7]

Immunosuppressive medications that have been associated with PML include cyclophosphamide, corticosteroids, mycophenolate mofetil and monoclonal antibodies including natalizumab (Tysabri), rituximab (Mabthera) and alemtuzumab (MabCampath).[8] The Australian Product Information for both rituximab and natalizumab carries a black box warning on the risk of PML.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

How is PML diagnosed?

Diagnosis should be considered in any patient with risk factors who presents with progressive neurological signs or symptoms and has MRI evidence of multiple characteristic lesions. The early signs of PML are often related to cognitive dysfunction, manifesting as mental slowness, disorientation and behavioural changes.[2] Motor and sensory disturbance, characterised by lack of coordination, gait disturbance, ataxia, hemiparesis or visual deficits may also be found at the time of presentation.[2] Seizures, language difficulties and headaches can occur but are less common. These signs and symptoms progress over the course of a few weeks and death can occur weeks to months after diagnosis.

The diagnosis can be confirmed by detection of JC virus DNA or proteins using in situ hybridisation or immunohistochemistry on a brain biopsy sample, or by detection of JC virus DNA in the cerebrospinal fluid by quantitative polymerase chain reaction.[3] However, a negative polymerase chain reaction result does not exclude the diagnosis of PML, particularly early in the disease.

How many cases have been reported?

A search of the Australian and New Zealand adverse event databases found 28 reports of PML (Table). Many of these cases had multiple risk factors including prior or concomitant immunosuppression therapies, underlying disease and chemotherapy. The majority of reports were associated with the monoclonal antibodies, rituximab and natalizumab. However, this may be due to greater awareness of PML in association with these particular medicines.

Table
Australian and New Zealand reports of PML associated with immunomodulatory medicines, to 30 November 2012

Medicine	No. of reports
Rituximab*	13
Natalizumab	13
Alemtuzumab	1
Cyclophosphamide*	1
Prednisolone*	1
Mycophenolate mofetil#	1
Tacrolimus#	1
Dexamethasone#	1

* Co-suspect medicines in same report
# Co-suspect medicines in same report

How is PML treated?

Improved chance of survival is associated with early diagnosis, younger age at diagnosis and if the disease is limited to one lobe of the brain.[1]

Current treatment of PML is limited and is generally supportive in nature.

The current treatment strategy for PML in HIV-negative patients is to restore the host adaptive immune response by stopping or decreasing immunosuppression.[3] There are currently no specific antiviral drugs for the JC virus.

Recovery of the immune system can trigger immune reconstitution inflammatory syndrome (IRIS). In HIV-negative patients with PML-IRIS, the current treatment is corticosteroids to reduce the inflammatory response.[3]

Key messages

- PML is a rare but potentially fatal disease
- Patients with compromised immune systems due to immunomodulatory medicines or disease are at risk of developing PML
- A diagnosis of PML should be considered for any patient with risk factors who presents with progressive neurological signs or symptoms
- Early diagnosis is associated with an improved chance of survival

Conjointly prepared by the TGA and Medsafe (the New Zealand Medicines and Medical Devices Safety Authority)

REFERENCES

1. Vermersch P, Kappos L, Gold R, Foley JF, Olsson T, Cadavid D, et al. Clinical outcomes of natalizumab-associated progressive multifocal leukoencephalopathy. Neurology 2011;76:1697-704.
2. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. Annu Rev Med 2010;61:35-47.
3. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010;9:425-37.
4. Berger JR, Khalili K. The pathogenesis of progressive multifocal leukoencephalopathy. Discov Med 2011;12:495-503.
5. Tyler KL. Progressive multifocal leukoencephalopathy: can we reduce risk in patients receiving biological immunomodulatory therapies? Ann Neurol 2010;68:271-4.
6. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy: a national estimate of frequency in systemic lupus erythematosus and other rheumatic diseases. Arthritis Rheum 2009;60:3761-5.
7. Holman RC, Torok TJ, Belay ED, Janssen RS, Schonberger LB. Progressive multifocal leukoencephalopathy in the United States, 1979-1994: increased mortality associated with HIV infection. Neuroepidemiology 1998;17:303-9.
8. Piccinni C, Sacripanti C, Poluzzi E, Motola D, Magro L, Moretti U, et al. Stronger association of drug-induced progressive multifocal leukoencephalopathy (PML) with biological immunomodulating agents. Eur J Clin Pharmacol 2010;66:199-206.

MEDICINES SAFETY UPDATE

Thyroxine (Eutroxsig and Oroxine) and fractures

Health professionals are advised that the Product Information for thyroxine has recently been updated to include a precaution about the increased risk of osteoporotic fracture associated with excessive thyroxine doses. Control of hypothyroidism should be monitored regularly, especially in the elderly, and the thyroxine dose adjusted accordingly.

Chronic hyperthyroidism promotes bone turnover, characterised by increases in bone resorption and in urinary excretion of calcium and phosphorus. Increased bone resorption may result in osteoporosis and an increased risk of fracture. A similar risk appears to exist for hypothyroid patients receiving higher-than-needed doses of thyroxine. The elderly may be at particularly increased risk, since thyroxine replacement needs decrease with age, and age is an additional risk factor for osteoporosis.[1]

Fracture risk with thyroxine replacement therapy

Two recent large studies have examined the risk of fracture in patients on long-term thyroxine replacement. A nested case-control study in 213 511 Canadian thyroxine users aged over 70 followed patients for a mean of 3.8 years.[1] Thyroxine use was classified as high (>93 microgram), medium (44–93 microgram) or low dose (<44 microgram daily) based on cumulative dose over the preceding 12 months. Among current (at the time of fracture) thyroxine users, high thyroxine doses were associated with a 3.5-fold increased risk of fracture, and medium doses with a 2.6-fold increased risk, compared to low doses. Both these results were statistically significant. The study did not check for appropriateness of thyroxine use by measuring thyroid stimulating hormone (TSH) levels.

An observational cohort study in 17 684 Scottish thyroxine users aged 18 and over, with a median follow-up of 4.5 years, classified patients according to their mean TSH level over time, into suppressed (TSH ≤0.03 mU/L), low (0.04–0.4 mU/L), normal (0.4–4.0 mU/L) and high (>4.0 mU/L).[2] Compared to patients with normal TSH, there was a statistically significant two-fold increased risk of hospitalisation or death due to osteoporotic fracture in patients with suppressed TSH. There was no significant increase in risk for patients with a low (but not suppressed) TSH.

Although neither study measured both thyroxine and TSH levels, each found an association between either high or excessive (as measured by TSH suppression) thyroxine dose and fracture. As well as increasing the risk of osteoporosis, excess thyroxine may also increase the risk of falls secondary to arrhythmia or muscle weakness, particularly in the elderly.[1]

Information for health professionals

Health professionals are advised that the Product Information for thyroxine (Oroxine, Eutroxsig) has recently been updated with a new precaution about the effects of thyroxine on bone mineral density. It is recommended that patients receiving thyroxine are given the minimum dose necessary to achieve the desired clinical and biochemical response. Prescribers should keep in mind that replacement thyroxine needs decrease in the elderly and serum TSH should be monitored regularly and thyroxine doses adjusted accordingly. The risk of fracture may be greater in patients with other risk factors for osteoporosis, including postmenopausal women, those with a family history or past history of fracture or osteoporosis, smokers, and patients with vitamin D deficiency.

REFERENCES

1. Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon PA, et al. Levothyroxine dose and risk of fracture in older adults: nested case-control study. BMJ 2011;342:d2238.
2. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. J Clin Endocrinol Metab 2010;95:186-193.

Oral bowel cleansing products – serious electrolyte disturbances

The use of oral bowel cleansing products is part of the preparation for a number of medical, diagnostic and surgical procedures. These products create a cathartic effect by osmotic action, resulting in a transfer of fluid and electrolytes to the gut lumen. Marked dehydration, electrolyte abnormalities and associated complications may occur as a result in otherwise well patients. The TGA has previously alerted prescribers to the risk of severe electrolyte disturbances in association with the use of sodium picosulfate-containing products.[1]

Since January 2002 the TGA has received a total of 51 adverse event reports for these products, of which 18 were reports of serious electrolyte disturbances. One of these reports was of a 60-year-old patient who experienced a cardiac arrest, one was of a 50-year-old patient who sustained permanent hypoxic brain damage as a result of serious adverse events following hyponatraemia, and a third report was of a 38-year-old who developed hyponatraemic encephalopathy.

While it is known that the elderly, the frail and those with cardiac failure or renal impairment are potentially at higher risk of an adverse event, health professionals are reminded that serious adverse events can occur in patients under the age of 60 years who are otherwise fit and healthy, and that this should be considered when prescribing/dispensing these products. All patients should be reminded of the importance of hydration and electrolyte replacement while taking these products and to seek medical attention if they experience any signs of severe dehydration, such as excessive thirst, dizziness, confusion and decreased urine output or dark coloured urine.

REFERENCE

1. Electrolyte disturbances with sodium picosulfate bowel cleansing products. Aust Adv Drug React Bull 2002;21:1.

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

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

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

Reports may be submitted:

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

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

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ARTICLE

The safety of leflunomide

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SUMMARY

Leflunomide, alone or in combination with other antirheumatic drugs, is an effective but potent immunosuppressive drug for patients with moderate to severe rheumatoid or psoriatic arthritis.

Common adverse effects include diarrhoea, nausea, vomiting, mouth ulcers, skin rash, alopecia, minor infections, mild increase in blood pressure and elevated liver enzymes.

Major adverse effects such as significant lung injury, severe infection and cytopenia may occur, and early recognition of these is crucial.

The risk of adverse effects is increased with concurrent medications, particularly methotrexate, and patient factors such as alcohol consumption and low body weight.

Regular monitoring with clinical assessment, blood counts and liver function tests is essential.

Leflunomide is contraindicated in pregnancy and effective contraception is required for men and women during and after treatment.

Live vaccines should be avoided for at least six months after stopping treatment.

Leflunomide has a complicated pharmacological profile, including a long half-life that makes the management of toxicity difficult.

Introduction

Leflunomide is an immunosuppressive drug with an anti-inflammatory action. It inhibits the biosynthesis of pyrimidine in rapidly dividing cells and is used as a disease-modifying antirheumatic drug (DMARD) in patients with rheumatoid and psoriatic arthritis. Leflunomide was listed on the Pharmaceutical Benefits Scheme (PBS) for rheumatoid arthritis in 2000 and for psoriatic arthritis in 2007. The rate of initial prescriptions was rapid due to the large number of patients with intolerance or lack of response to other DMARDs, including methotrexate. Also, there had been no other new disease-modifying drugs for rheumatoid arthritis in the preceding decade.

Leflunomide use in Australia [1]

It is estimated that more than 15 000 patients have received PBS-subsidised leflunomide in the last decade. The pattern of use in Australia is unique, with more than 50% of patients with rheumatoid arthritis on leflunomide also taking methotrexate. This is in contrast to the USA and Europe, where rates of simultaneous prescribing are low (<10%).

While there is increasing recent evidence to support the benefits of aggressive combination DMARD therapy, the high co-prescription rate appears to have been primarily driven by the PBS eligibility requirements to access biological DMARDs, rather than by contemporary trial findings. Etanercept was first listed on the PBS for rheumatoid arthritis in August 2003. Until the modifications to eligibility criteria in August 2010, to qualify for subsidised etanercept patients had to have already had:

- weekly methotrexate (at least 20 mg),
- a combination of methotrexate and two other DMARDs, and
- leflunomide (with or without methotrexate) or cyclosporin.

For most patients leflunomide was added to pre-existing methotrexate, hence the high rate of co-prescription in Australia. There is variability in opinions amongst rheumatologists as to whether or not the doses of leflunomide and methotrexate should be reduced by 30–50% of the maximum recommended daily dose when combination treatment is started.

Clinical pharmacology

Leflunomide is a prodrug which is rapidly metabolised in the liver and gut wall to the active metabolite teriflunomide or A771726. Its half-life of 2–4 weeks means a loading dose was used in the clinical trials to have a clinical effect as quickly as possible – without this, it may take up to two months to take effect. However, a loading dose is not typically used in current practice because of the increased risk of adverse effects, particularly gastrointestinal intolerance.

Leflunomide's long half-life means adverse effects and drug interactions may persist for several weeks after cessation. The active metabolite undergoes extensive enterohepatic recirculation and is eliminated by biliary and renal excretion. If major toxicity or unplanned pregnancy occurs, a washout procedure is undertaken with oral cholestyramine (typically

8 g three times daily for 11 days) or activated charcoal. Teriflunomide cannot be removed by dialysis therefore haemodialysis is not a treatment approach for patients who are experiencing major toxicity or who have taken an overdose of leflunomide.

Safety concerns

In clinical studies lasting two years, the most common adverse effects (in more than 5% of patients) included diarrhoea, nausea, vomiting, mouth ulcers, skin rash, alopecia, minor infections, mild increase in blood pressure and asymptomatic reversible liver enzyme increases. However, concerns have been raised about the risk of major adverse effects and early recognition of leflunomide's potential toxicity.[2]

The Adverse Drug Reactions Advisory Committee (ADRAC)* received reports of severe pulmonary disease and other serious hepatic, haematological and neurological adverse effects.[3] It is unclear whether the apparently high number of spontaneously reported serious adverse effects in Australia relates to the high concurrent DMARD prescription rate, an epidemiological phenomenon, reporting bias, or a combination of these factors.

A failure to recognise the possibility of leflunomide-induced lung disease led to a review by the regulatory authorities and the recommendation for an educational update to medical practitioners.

Lung injury

Interstitial lung disease (including interstitial pneumonitis and pulmonary fibrosis) has been rarely reported (less than 0.38% of patients) during treatment with leflunomide.[4] The two most common symptoms of lung injury are shortness of breath, particularly with exertion, and a dry cough. Additional symptoms may include fever, fatigue and generalised myalgia. The symptoms may occur acutely during therapy or develop insidiously. The onset of new or worsening of pre-existing respiratory symptoms such as cough or dyspnoea should prompt further investigation. Although lung injury has been associated with both leflunomide and methotrexate taken alone, the risk of interstitial pneumonitis appears to be increased when the drugs are taken concurrently.[5–7]

A multivariate analysis of more than 5000 Japanese patients prescribed leflunomide identified pre-existing interstitial pneumonitis, use of a loading dose, cigarette smoking and low patient body weight as significant risk factors for the development of leflunomide-induced lung injury.[8]

When significant drug-related lung injury is suspected, the drug should be stopped immediately and washout treatment with cholestyramine is recommended.[9] However, the evidence of its benefit is inconclusive to date. High serum C-reactive protein, low serum albumin, severe hypoxaemia and mechanical ventilation indicate poor prognosis. Peripheral blood lymphopenia often occurs in association with lung injury and a sustained low lymphocyte count portends a fatal outcome.[4]

Significant infections

Patients with rheumatoid arthritis have an increased risk of morbidity and mortality related to infections. This may occur due to the disease itself or as a result of drugs used to control the disease.

In the controlled trials, respiratory infection (including bronchitis and pneumonia) was observed in 15% of patients treated with leflunomide over a six-month period. Respiratory infections, especially upper respiratory tract infections, are the most commonly reported site of infection followed by urinary tract, and skin or soft tissue infections. Over two-thirds of infections were mild or moderate in severity, however, serious infections (3.3 per 100 patient-years) including pneumocystis pneumonia and tuberculosis have been reported.[10]

Rarely, some patients develop fulminant, and even fatal, sepsis. The risk of severe infection is greatest in patients with severe rheumatoid arthritis, or in those receiving combination DMARD therapy or continuous prior corticosteroid use (oral prednisone >5 mg/day).

As teriflunomide has a direct inhibitory effect on proliferating T-lymphocytes, there is also a risk of new or reactivated herpetic infections such as shingles and oral or genital herpes simplex infection.

Hepatic dysfunction

Although leflunomide alone or in combination with other DMARDs is associated with elevations of liver enzymes (alanine aminotransferase and aspartate aminotransferase), most are less than two times the upper limit of normal, are transient or resolve with dose reduction. Rare cases of severe liver injury, some with fatal outcome, have been reported. Most cases occurred within six months and in patients with multiple risk factors for hepatotoxicity.

Patients should be counselled to have no or minimal alcohol (<3–4 standard drinks per week) and should avoid binge drinking. Concurrent use of other potentially hepatotoxic medications such as methotrexate should be monitored, as should over-the-counter, herbal and naturopathic medicines. Caution should be advised with current or recent hepatitis.

* In 2010, ADRAC was replaced by the Advisory Committee on the Safety of Medicines (ACSOM)

Neurological dysfunction

Up to 18% of patients with rheumatoid arthritis report paraesthesia from entrapment neuropathy, a mild distal symmetric predominantly sensory neuropathy, mononeuritis multiplex or severe sensory motor neuropathy. In addition, leflunomide-induced peripheral neuropathy has been noted with paraesthesia reported in 2.9%. Some data suggest patients who discontinue within 30 days of symptoms are more likely to improve or recover than patients who continue the drug.

Cytopenia

Leflunomide can impair marrow function. The risk of impairment is increased in older patients and when leflunomide is combined with methotrexate. Regular monitoring will identify problems promptly. Minor depressions of white blood cells/neutrophils are common but significant abnormalities are rare.

Hypertension

Leflunomide-related hypertension has been noted in up to 10% of patients. It can aggravate pre-existing hypertension or induce new-onset hypertension within three months of therapy. Most experts consider hypertension to be manageable during treatment with either a maintained or reduced dose of leflunomide, and by giving antihypertensive treatment.

Alopecia

Dose-dependent alopecia is a common transitory adverse effect of leflunomide and occurs in 6–23% of patients. Hair loss is diffuse and often mild to moderate. It seems prudent to reduce the leflunomide dose.

Skin conditions

Pruritus and a variety of skin conditions have been reported. These include a non-specific rash, isolated pruritus, mucosal ulcers, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichenoid reaction, cutaneous vasculitis, erythema multiforme and subacute cutaneous lupus.

Gastrointestinal toxicity

Diarrhoea is the most common adverse effect, occurring in 17% of trial patients. It is common when loading doses of 100 mg/day for three days are given, so Australian rheumatologists usually omit the loading dose. The majority of cases resolve with time and can be managed symptomatically. The exact mechanism of leflunomide-induced diarrhoea is not known.

Monitoring leflunomide therapy

All patients prescribed leflunomide must be monitored regularly during treatment. Current Australian practice follows British and American recommendations of blood pressure check, full blood count, urea and electrolyte tests, and liver function assessment before starting treatment. If blood pressure is greater than 140/90 mmHg on two consecutive readings two weeks apart, hypertension should be treated before starting leflunomide. During therapy, full blood count and liver function should be checked every month for the initial six months and if stable, 2–3 monthly thereafter. If leflunomide is co-prescribed with methotrexate or other potentially hepatotoxic medication or an immunosuppressant, monitoring should be monthly. After six months of combination treatment, patients should be monitored at least every 2–3 months thereafter. Guidelines for managing adverse events associated with leflunomide are listed in the Table.

Interaction with other medications

Caution should be exercised with drugs metabolised via cytochrome P450 2C9, such as warfarin and phenytoin. Leflunomide may reduce the metabolism of warfarin, thereby increasing the INR and risk of bleeding. Because of the active metabolite's long half-life, the effects of an interaction may persist for 2–4 weeks after stopping the drug. No significant interactions between leflunomide and triphasic oral contraceptives or cimetidine have been found. Smoking increases leflunomide clearance and this may be of particular relevance as several studies have shown smoking adversely influences the severity of rheumatoid arthritis.

Vaccination

Influenza and pneumococcal vaccinations are recommended for patients before starting leflunomide. Hepatitis B vaccination should be given if risk factors are present and vaccination has not previously been administered. No clinical data are available on the efficacy and safety of live vaccinations during leflunomide treatment. The US Food and Drug Administration recommends not using live vaccines during treatment and for at least six months after ceasing therapy.

Pregnancy and lactation

As animal studies with leflunomide showed an increase in teratogenicity and embryonic death, leflunomide is contraindicated in pregnancy. Conception should be excluded before commencing leflunomide treatment. Because of the long half-life, the sponsor advises ceasing leflunomide at least two years before a planned pregnancy or to use a washout procedure if inadvertent pregnancy occurs. A prospective cohort study (1999–2009) showed that 64 women with rheumatoid arthritis who were

exposed to leflunomide during pregnancy had a similar incidence of major infant abnormalities (5.3% of infants) compared to 108 pregnant women with rheumatoid arthritis not treated with leflunomide (5.3% of infants) and 78 healthy pregnant women (4.2% of infants). Similarly, no particular type of birth defects was treatment related.[11] Breastfeeding is not recommended with leflunomide.

Men taking leflunomide should avoid getting their partner pregnant while taking leflunomide and for up to 64 days after therapy (at least one cycle of spermatogenesis).[12]

Recommendations

Patients should be warned about the potential for mild adverse effects with leflunomide. The possibility of serious pulmonary, hepatic, haematological and neurological adverse effects should also be discussed. The necessity for regular blood monitoring should be emphasised. Leflunomide should be ceased if there is concern about possible adverse effects. ⋖

Dr Kubler is Chair of the Editorial Executive Committee of Australian Prescriber.

Table **Managing adverse reactions to leflunomide**

Adverse event	Action to be taken
Cytopenia	Minor depressions of white blood cells or neutrophils can be rechecked at 2–4 weeks. Cessation of leflunomide and washout with cholestyramine therapy may be recommended, depending on the severity of the cytopenia or presence of concurrent significant infection.
White cell count <3.5 x 10^9/L, neutrophils <2.0 x 10^9/L or platelets <150 x 10^9/L	Withhold drug until discussion with rheumatologist
Aspartate aminotransferase/alanine aminotransferase elevations	Ask patient about other potential hepatotoxin exposure such as recent alcohol use
<2 times the upper limit of normal	Observe patient and repeat liver function test within 1 month
2–3 times the upper limit of normal	If current dose is more than 10 mg/day, reduce to 10 mg/day and re-check weekly until normalised If enzymes are returning to normal, leave the patient on 10 mg/day If they remain elevated, stop leflunomide and discuss with rheumatologist
>3 times the upper limit of normal	Stop leflunomide and re-check within 3–7 days. If they are still high, withdraw treatment and consider washout.
Rash or itch	Consider dose reduction with or without antihistamines. If severe, stop and consider washout.
Hair loss	Consider dose reduction. If severe, cease drug.
Abnormal bruising or severe sore throat	Check full blood count immediately and withhold drug until results are available
Headache	If severe, consider dose reduction. If severe headaches persist, stop and consider washout.
Gastrointestinal upset (nausea, diarrhoea)	If loading dose has been used, give symptomatic treatment. If steady state has been reached, give symptomatic treatment and consider dose reduction. If symptoms are severe or persistent, stop and consider washout.
Weight loss	Monitor closely. If more than 10% weight loss with no other cause identified, reduce dosage or stop and consider washout.
New or increasing breathlessness or dry cough	Consult with the specialist urgently. Consider stopping leflunomide immediately and washout.
Hypertension	Maintain or reduce dose and give antihypertensive treatment

SELF-TEST QUESTIONS

True or false?

5. Concomitant methotrexate, use of a leflunomide loading dose and low body weight are risk factors for lung injury in patients receiving leflunomide.

6. After stopping leflunomide treatment, the active metabolite is cleared within two weeks.

Answers on page 35

REFERENCES

1. Public Summary Document. Leflunomide. Department of Health and Ageing. 2007 Mar. www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-leflunomide-mar07 [cited 2013 Jan 7]
2. Is it leflunomide lung? Aust Adv Drug React Bull 2009;28:15.
3. Leflunomide: serious hepatic, blood, skin and respiratory reactions. Aust Adv Drug React Bull 2001;20:7.
4. Sato T, Inokuma S, Sagawa A, Matsuda T, Takemura T, Otsuka T, et al. Factors associated with fatal outcome of leflunomide-induced lung injury in Japanese patients with rheumatoid arthritis. Rheumatology (Oxford) 2009;48:1265-8.
5. Savage RL, Highton J, Boyd IW, Chapman P. Pneumonitis associated with leflunomide: a profile of New Zealand and Australian reports. Intern Med J 2006;36:162-9.

6. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum 2006;54:1435-9.
7. Chikura B, Lane S, Dawson JK. Clinical expression of leflunomide-induced pneumonitis. Rheumatology (Oxford) 2009;48:1065-8.
8. Sawada T, Inokuma S, Sato T, Otsuka T, Saeki Y, Takeuchi T, et al. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology 2009;48:1069-72.
9. Chakravarty K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008;47:924-5.
10. Jenks KA, Stamp LK, O'Donnell JL, Savage RL, Chapman PT. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol 2007;34:2201-3.
11. Chambers CD, Johnson DL, Robinson LK, Braddock SR, Xu R, Lopez-Jimenez J, et al. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum 2010;62:1494-503.
12. Brent RL. Teratogen update: reproductive risks of leflunomide (Arava); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. Teratology 2001;63:106-12.

New drugs

Aflibercept

Approved indication: neovascular age-related macular degeneration

Eylea (Bayer)

single-use vials containing 40 mg/mL solution for intravitreal injection

Australian Medicines Handbook Appendix A

Neovascular or 'wet' age-related macular degeneration is the most severe form of the disease (see Aust Prescr 2012;35:90-3). Although it only accounts for 10% of all cases of age-related disease, it is responsible for 90% of severe visual loss. It occurs when abnormal blood vessels develop under the macula and leak fluid and blood. This eventually leads to scarring and permanent loss of central vision.

Vascular endothelial growth factor A (VEGF-A) is a key mediator in neovascular age-related macular degeneration. The standard VEGF inhibitor used in this disease is ranibizumab, a monoclonal antibody fragment (see Aust Prescr 2007;30:79-82). Aflibercept is a fusion protein that blocks the binding of VEGF-A to its receptors by acting as a soluble decoy receptor. Aflibercept also blocks placental growth factor which is thought to play a role in the disease.

Table **Efficacy of aflibercept in the VIEW 1 and 2 clinical trials**

Treatment (52 weeks)	Proportion of patients who lost fewer than 15 letters of visual acuity	
	VIEW 1	VIEW 2
Aflibercept 2 mg every month for 3 months then every 8 weeks	94.4%	95.4%
Aflibercept 2 mg every 4 weeks	95.1%	94.5%
Aflibercept 0.5 mg every 4 weeks	95.0%	95.3%
Ranibizumab 0.5 mg every 4 weeks	93.8%	94.9%

Values taken from the Australian Public Assessment Report (AusPAR)

The approval of aflibercept is based on two 52-week comparative trials with ranibizumab – VIEW 1 and VIEW 2. In summary, over 2400 patients were equally randomised to one of four treatment regimens (see Table). The primary outcome of the trials was the percentage of patients who maintained their vision. This was defined as losing less than 15 letters of visual acuity on the chart used in the Early Treatment Diabetic Retinopathy Study. The chart consists of 14 rows of 5 letters each. The efficacy of aflibercept 2 mg given by intravitreal injections at four or eight week intervals and 0.5 mg monthly was similar to monthly ranibizumab 0.5 mg (Table). The recommended dose of aflibercept is 2 mg every eight weeks following three initial monthly injections.

Adverse effects in the trials were mainly ophthalmic. The most common were conjunctival haemorrhage (24.7%), cataract (6.8%), eye pain (8.7%), vitreous detachment (6%), vitreous floaters (5.9%) and increased ocular pressure (5.2%). The incidence of these events was similar with ranibizumab.

Although rare, endophthalmitis has been reported after intravitreal injection with aflibercept so correct aseptic technique should always be used. Aflibercept is contraindicated in patients with ocular or periocular infection or severe intraocular inflammation.

Although aflibercept has not been tested in pregnant or lactating women, fetal abnormalities have occurred in animals when it was given systemically. Aflibercept is not recommended in pregnancy or lactation.

The safety and efficacy of aflibercept injected every eight weeks (following three initial monthly injections) for 12 months seems to be comparable to ranibizumab injected every four weeks, so patients may prefer it. Adverse effects were confined to the eye and appeared to be related to the intravitreal injections.

T manufacturer provided the product information

REFERENCES *†A

None

First published online 3 December 2012

Mifepristone

Approved indication: termination of pregnancy
Mifepristone Linepharma (MS Health)
200 mg tablets
Australian Medicines Handbook Appendix A

Mifepristone is an antiprogestogen which competes with progesterone at its receptor. In pregnant women mifepristone's action on the uterus can induce abortion. It causes dilatation of the cervix and increases the sensitivity of the myometrium to the action of prostaglandins. As not all women will abort with mifepristone alone, they are given the prostaglandin misoprostol 36–48 hours after mifepristone.[1]

The recommended dose of mifepristone is a single 200 mg tablet. This is rapidly absorbed. Mifepristone is metabolised by cytochrome P450 3A4, but no interaction studies have been carried out. Some of the metabolites may also act on the progesterone receptor. The final half-life of mifepristone and its metabolites may be up to 90 hours, with most of the dose being excreted in the faeces. Due to a lack of data, mifepristone is not recommended for women with renal failure or hepatic impairment. As the drug has some action on glucocorticoid receptors, adrenal failure is a contraindication. Patients taking corticosteroids, including inhaled corticosteroids, may need to increase their dose.

As mifepristone was first developed in the 1980s, it has been studied in several different regimens and in different stages of pregnancy. A systematic review of medical methods of abortion in the first trimester found that, in combination with a prostaglandin, the 200 mg dose of mifepristone was as effective as a 600 mg dose.[2] In one trial 89.3% of 792 pregnant women, with a menstrual delay of 35 days or less, had a complete abortion after taking mifepristone 200 mg followed by oral misoprostol. The median time to abortion was 51 hours after taking mifepristone.[3]

Beyond the first trimester, mifepristone can be used to prepare for termination of pregnancy, for medical reasons, with prostaglandins. A systematic review of medical methods of second trimester abortion concluded that mifepristone with misoprostol had the highest efficacy.[4] As the efficacy of the combination declines with gestational age[3], up to 30% of women may still need surgical evacuation when the drugs are used after the first trimester.

Although mifepristone has only recently been registered in Australia, it has been used for early medical abortion. An observational study involving 13 345 women used a regimen of oral mifepristone 200 mg followed 24–48 hours later by buccal misoprostol 800 microgram (gestational age ≤63 days). The method only failed in 3.5% of patients, with 2.9% needing surgical evacuation and 0.6% continuing the pregnancy.[5]

The combination of mifepristone and misoprostol commonly causes nausea, vomiting and diarrhoea. Vaginal bleeding is to be expected, but this can be prolonged. In the Australian study the incidence of haemorrhage requiring transfusion was approximately 0.1%.[5] The method is not recommended in women with anaemia. Infection is another potential complication of abortion and one woman died in the Australian study.[5] It is therefore important that women are advised what symptoms to expect and that they are followed up to ensure the abortion is complete and uncomplicated. If the method fails and the woman decides to continue with the pregnancy there is uncertainty about the effects of the drugs on the surviving fetus.

Ectopic pregnancy is a contraindication to mifepristone. If the woman has become pregnant despite having an intrauterine contraceptive device, the device should be removed before mifepristone is used.

In the Australian study most of the women reported medium or heavy bleeding and moderate or severe pain. However, 78% said they would choose the same method again.[5] There is limited evidence comparing medical versus surgical abortion. In a randomised trial involving 122 women who were 13–20 weeks pregnant, pain was rated as moderate to severe by 43% of those who had mifepristone and misoprostol and 23% of those who had surgery. While the women were equally satisfied with their care, only 53% would choose medical abortion again, whereas 100% of the surgical group would choose surgery again.[6]

Although it has taken a long time for mifepristone to be approved in Australia, it has been used in parts of Europe for over 20 years. It adds to the options available when abortion is being considered. While the Australian study showed mifepristone with misoprostol is generally safe for outpatient treatment in early pregnancy, the method will not be suitable for all women. Some will present after the limit of 49 days gestation given in the Australian product information. If mifepristone and misoprostol are used, access to emergency care and follow-up are essential.

T manufacturer provided the product information

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

REFERENCES *†

1. Healy DL. Mifepristone: an overview for Australian practice. Aust Prescr 2009;32:152-4.
2. Kulier R, Kapp N, Gulmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev 2011;CD002855.
3. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation. BJOG 2000;107:524-30.
4. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev 2011;CD005216.
5. Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: a large Australian observational study. Med J Aust 2012;197:282-6.
6. Kelly T, Suddes J, Howel D, Hewison J, Robson S. Comparing medical versus surgical termination of pregnancy at 13-20 weeks of gestation: a randomised controlled trial. BJOG 2010;117:1512-20.

First published online 3 December 2012

Teriflunomide

Approved indication: multiple sclerosis

Aubagio (Sanofi-aventis)

14 mg film-coated tablets

Australian Medicines Handbook section 16.5

The inflammatory demyelination of multiple sclerosis is thought to be the result of an autoimmune disorder. In recent years drugs which alter the immune system have been used to try and prevent the progression of disability. Immunomodulating drugs such as interferon beta and glatiramer have to be injected, but an oral drug, fingolimod, was marketed in 2011. Teriflunomide is another oral drug for relapsing forms of multiple sclerosis. It is the active metabolite of leflunomide, an immunosuppressant used in rheumatoid arthritis.

Teriflunomide is taken once a day. It takes approximately three months for the plasma concentration to reach a steady state. Most of the drug is excreted unchanged in faeces, but some metabolites are excreted in the urine. The median half-life of the drug is 18–19 days.

The main trial of teriflunomide involved 1088 adults, aged under 55 years, who had had relapsing multiple sclerosis for a mean of 8.7 years. They were randomised to take teriflunomide 7 mg, 14 mg or a placebo for 108 weeks (796 patients completed the study). Both doses of teriflunomide significantly reduced the relapse rate. The increase in the number and size of lesions seen with MRI was significantly less with teriflunomide.[1]

Adverse events were common in all three treatment groups. These led to treatment being stopped by 9.8% of the patients taking teriflunomide 7 mg, 10.9% of those taking 14 mg and 8.1% of the placebo group. Nausea, diarrhoea and thinning of the hair were more frequent with teriflunomide than with placebo.

Leflunomide is known to be associated with liver failure, so patients taking teriflunomide need frequent monitoring of liver function. In the clinical trial 12–14% of patients had increased concentrations of alanine aminotransferase (ALT).[1] In the USA, teriflunomide is not recommended for patients who have ALT concentrations more than twice the upper limit of normal. As it may take up to two years for teriflunomide to be eliminated, patients who develop liver problems will need to be treated with charcoal and cholestyramine to speed up elimination.

This elimination procedure is also recommended for women trying to conceive. Animal studies have found that teriflunomide is teratogenic, so reliable contraception is essential.

Teriflunomide can reduce the white blood cell count which could increase the risk of infection. Patients should be screened for tuberculosis before treatment and live vaccines are not recommended. There is an interaction with warfarin which reduces the INR.

In the trial, blood pressure increased in 5–5.4% of the patients given teriflunomide, compared with 3.1% of the placebo group.[1] Hyperkalaemia, acute renal failure and peripheral neuropathy also occur.

Some of the adverse effects are predictable because of teriflunomide's relationship with leflunomide. Like leflunomide, it could potentially cause interstitial lung disease and serious skin reactions.

Most patients will have adverse events, but not all will benefit. During the trial approximately 54–57% of the patients taking teriflunomide were relapse free, compared with 46% of the placebo group. The 31% relative reduction in the rate of relapse only equates to a difference of 0.17 in the annual relapse rate (placebo 0.54 vs teriflunomide 0.37). Disability progressed in 20–27% of the patients, with no significant difference between placebo and teriflunomide 7 mg (27.3% vs 21.7%). Treatment had no significant impact on the patients' fatigue.[1]

Although it is difficult to compare studies, the annualised relapse rate with fingolimod was 0.16–0.18 (placebo 0.4), a relative reduction of 54–60%.[2] While the drugs have a modest effect on relapses, this benefit has to be balanced against the need for regular monitoring and the risk of serious adverse reactions.

T T manufacturer provided additional useful information

REFERENCES *

1. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365:1293-303.

2. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.

First published online 20 December 2012

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

* 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)

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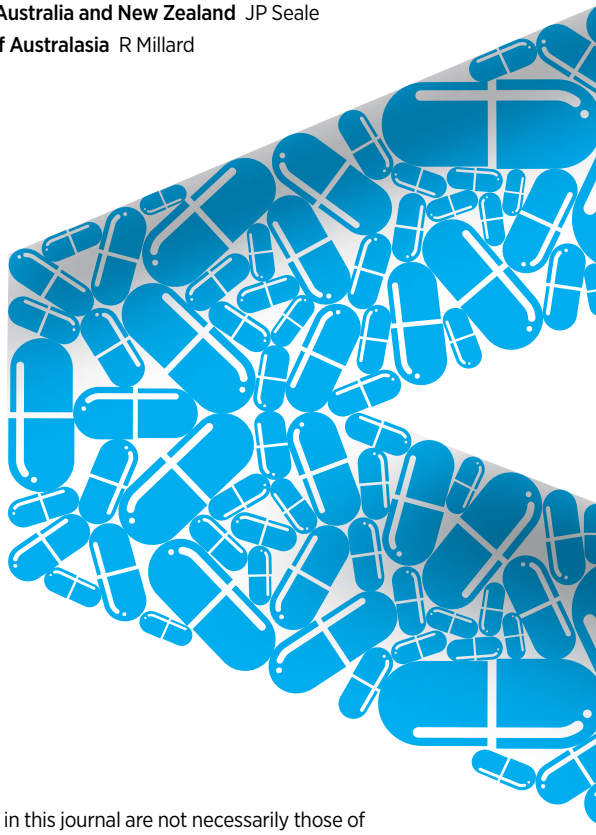

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