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EDITORIAL

Improving transparency in the pharmaceutical industry

Deborah Monk
Director
Compliance
Medicines Australia
Canberra

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Medicines Australia represents many of the companies that develop new prescription medicines. It believes that companies' interactions with Australian healthcare professionals have a high degree of ethical integrity. This stems from both the Medicines Australia Code of Conduct[1] and complementary ethical standards developed and adopted by the professions. Based on these ethical standards, there should be a high level of community trust in the industry and healthcare professionals. However, interactions between pharmaceutical companies and healthcare professionals have been subject to negative perceptions. This is despite changes to the Code of Conduct over the last decade.

As an industry, we need to take some responsibility for these negative perceptions and any resulting erosion of trust. We have not done as good a job as we might have in explaining why companies and healthcare professionals interact, how they interact, how our interactions contribute to better patient care and the standards industry adheres to when engaging with healthcare professionals. Medicines Australia seeks to uphold and strengthen community trust in the pharmaceutical industry and our engagement with healthcare professionals. One way Medicines Australia is doing this is by being more transparent about these interactions.

With the introduction of the latest edition of the Code of Conduct in May 2015,[1] the industry is striving to be more open, more transparent and more communicative about interactions between companies and healthcare professionals. The new Code requires Medicines Australia's member companies to publish information about individual healthcare professionals (including doctors, pharmacists, nurses, dentists and dietitians) who receive a 'reportable payment'. Reportable payments are fees for a healthcare professional's advice or service, such as an honorarium, consulting or sitting fee, and the provision of airfares, accommodation or registration fees to enable a healthcare professional to engage in education. The cost of food and beverages provided during educational meetings is not reportable for individual healthcare professionals. Reportable payments will be published every six months on companies' websites while Medicines Australia investigates establishing a central reporting system for all companies' reports.

Companies are responsible for reporting payments associated with company-initiated activities and meetings, whether these are organised directly or by another company or agency. If a company provides sponsorship to a college or society to hold its own educational meeting, these sponsorships will be separately reported, by event, in reports published on Medicines Australia's website.

When Medicines Australia developed the new Code of Conduct, there was considerable debate about whether healthcare professionals should be able to 'opt out' of their payments being reported. However, the Royal Australian College of General Practitioners, the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Psychiatrists, the Society of Hospital Pharmacists of Australia and consumer organisations such as the Consumers Health Forum of Australia had strong views against an 'opt-out' clause. Disclosing reportable payments will therefore become mandatory.

From 1 October 2015, Medicines Australia's member companies started to collect information about reportable payments to individual healthcare professionals. At first this information will only be publicly reported for each healthcare professional with their consent. The first reports will be published on companies' websites by 31 August 2016. After a year's transition, payments will be reported without seeking consent. Healthcare professionals will be notified of the reporting requirement when they receive a reportable payment. From 1 October 2016, healthcare professionals' details will be disclosed whenever a reportable payment is made.

The new measures are an important step forward for industry, healthcare professionals and importantly Australian patients. They are part of a movement towards more transparency which is also underway in the USA, across Europe and in Japan.

Medicines Australia supports greater transparency in companies' relationships with healthcare professionals. Our ultimate goal is for the degree of transparency required by the Medicines Australia Code of Conduct to be normal, expected business practice for the entire Australian medicines and medical devices industry. Medicines Australia would encourage and support other industry sectors, such as the medical devices, generic medicines, over-the-

counter medicines and complementary medicines, to follow this lead towards greater transparency about their interactions with healthcare professionals. <

Conflict of interest: Deborah Monk is Director, Compliance at Medicines Australia.

REFERENCE

1. Medicines Australia. Code of Conduct. 18th ed. 2015. https://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-current-edition [cited 2016 Jul 1]

EDITORIAL

Transparency is good, independence from pharmaceutical industry is better!

Agnes Vitry
Senior lecturer
School of Pharmacy and Medical Sciences
University of South Australia

Keywords
advertising, drug industry, Medicines Australia

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In Australia, the promotion of medicines to health professionals is controlled by self-regulatory schemes operated by the pharmaceutical industry. The Code of Conduct overseen by Medicines Australia covers prescription drugs marketed by member companies. The latest version of Medicines Australia's Code of Conduct (Edition 18) includes a requirement for greater transparency in the payments made to health professionals. The new requirements have been adopted reluctantly by the pharmaceutical industry and only following the lead of other countries, long-standing campaigns by medical and consumer organisations, and pressure from the Australian Competition and Consumer Commission (ACCC).

After several rounds of stakeholder consultation, the 18th edition of the Code was approved by the ACCC in April 2015. Approval was on the condition that all relevant 'transfers of value', either in kind or cash, such as speaking fees, advisory board fees, or sponsorships to attend conferences, would be reported and that the data would be accessible to the public.[1] There was an 'opt-out' clause whereby health professionals could choose not to have their name publicly reported, but this will be terminated in October 2016 when the reporting of payments becomes mandatory.

Still in contention is the establishment of a searchable database of all companies' payments to healthcare professionals that would allow members of the public to access information in a single location. From August 2016, data will only be available on each individual company's website, but the ACCC has requested that Medicines Australia develop and implement a centralised database.

There are still a number of unsatisfactory points in the current transparency provisions. Not all payments have to be reported. The Consumers Health Forum of Australia was disappointed that the reporting of hospitality costs, which was required by Edition 17 of the Code, was discontinued. Instead there is a limit of $120 ($132 including GST) per meal provided. In practice, no company will ever have to record or report a doctor receiving their hospitality if they stay under this limit. This means that an important part of the industry 'transfer of values' to health professionals will not be captured in the new system. There should be 'no free lunch'. Items of low monetary value could add up to a significant sum when aggregated over time, and have been shown to be extremely influential.[2]

The Society of Hospital Pharmacists of Australia also expressed concerns that the Code did not specifically address the relationship with healthcare organisations including support for professional development, sponsorship of national or international conferences and grants through third parties.[3] Payments in relation to research work including clinical trials are not reportable although many post-marketing studies (phase IV trials) are mainly promotional in nature and are known as 'seeding' trials. Furthermore, involving opinion leaders in clinical research is a key promotional strategy for the pharmaceutical industry which cannot be ignored.[4]

The Department of Health is also pushing for increasing transparency, in particular with regards to making information on medicines available, for example by publishing companies' submissions to the Pharmaceutical Benefits Advisory Committee. This proposal is fiercely opposed by the pharmaceutical industry which claims these data are 'commercial in confidence'.

Another important concern is that the transparency provisions do not apply to pharmaceutical companies that are not members of Medicines Australia. Another industry organisation, the Generic and Biosimilar Medicines Association (GBMA), which has opted out of ACCC Code authorisation, has just decided to remove the requirement for members to report on educational events and non-price benefits such as access to training events or patient information sheets.[5] In 2014–15 GBMA spent more than $2.2 million on non-price benefits to pharmacists and over $300 000 on educational events.[6] This backward step is a real concern as the generic and biosimilar market is growing rapidly in Australia.

Companies do not always adapt to new regulations in good ways. GlaxoSmithKline has announced that it will end direct payments to health professionals for speaking or attending medical conferences, but will use this budget to hire a new team of medical experts working at the global, national and local level.* This

* NPS MedicineWise is conducting educational activities supported by an independent educational grant from GlaxoSmithKline secured by VentureWise, a wholly owned commercial subsidiary of NPS MedicineWise. NPS MedicineWise has designed and developed the content with complete independence and editorial control.

strategy may provide more transparency, but still leaves medical education at extreme risk of being biased in favour of the company's own products.

The growing trend of product familiarisation programs and patient support programs in Australia is a real concern with almost no public information available on these programs. For example, Novo Nordisk is currently enrolling the pharmacy workforce as well as prescribers in a patient weight-loss support program promoting the use of Saxenda (liraglutide) through 'Saxenda Network Pharmacies'.[7] This drug is not covered by the Pharmaceutical Benefits Scheme and pharmacists may be able to claim a professional service fee from the manufacturer. It is unclear whether this fee will be reportable.

There is no evidence that information provided by the pharmaceutical industry improves prescribing practices.[8] Pharmaceutical promotion will always aim to influence the choice of prescribers towards newer, more expensive medicines and sometimes more risky medicines. In Australia, there is a wide range of independent sources of information on medicines including the Australian Medicines Handbook, Therapeutic Guidelines and *Australian Prescriber* that health professionals can consult.

A number of health professionals and organisations have already chosen to be independent from the pharmaceutical industry. Medical education in some hospitals such as Monash Health is now internally funded or funded by other organisations.[9]

The No Advertising Please campaign was launched by a group of health professionals and academics in 2014 and has won strong support from the Consumers Health Forum of Australia, the peak health consumer organisation in Australia. The campaign encourages doctors to avoid seeing drug representatives by pledging to not see them for one year.[10] The campaign's website also provides comprehensive information on research evidence showing that doctors who see drug representatives are more likely to prescribe more medicines, more expensive medicines and are less likely to follow clinical guidelines.

Transparency is good but independence from pharmaceutical industry is better for the health of patients and the healthcare system. ≺

Conflict of interest: none declared

REFERENCES

1. Australian Competition and Consumer Commission. Applications for revocation and substitution of authorisations A91436–A91440 lodged by Medicines Australia Limited in respect of the Medicines Australia Code of Conduct edition 18. 2015 Apr 24. http://www.csanz.edu.au/wp-content/uploads/2015/04/A91436-A91440-Revocation-and-Substitution-of-A91316-A91320-Medic....pdf [cited 2016 Jul 1]
2. Katz D, Caplan AL, Merz JF. All gifts large and small: toward an understanding of the ethics of pharmaceutical industry gift-giving. Am J Bioeth 2003;3:39-46. http://dx.doi.org/10.1162/15265160360706552
3. The Society of Hospital Pharmacists of Australia. Submission to the Australian Competition and Consumer Commission Medicines Australia Limited - Revocation and Substitution - A91436 - A91440. 2014. http://registers.accc.gov.au/content/index.phtml/itemId/1179619/fromItemId/278039/display/submission [cited 2016 Jul 1]
4. Flicker L. The influence of opinion leaders. Aust Prescr 2012;35:74-5. http://dx.doi.org/10.18773/austprescr.2012.031
5. Lam M. GBMA ends transparency reporting. Pharma in Focus. 2016 Feb 1. www.pharmainfocus.com.au [cited 2016 Jul 1]
6. Lam M. Generics spend $2.2m on pharmacists. Pharma in Focus. 2016 Jan 22. www.pharmainfocus.com.au [cited 2016 Jul 1]
7. Pharmacy key for Saxenda. Pharmacy Daily 2016 Feb 1. www.pharmacydaily.com.au/news/pharmacy-key-for-saxenda/50289 [cited 2016 Jul 1]
8. Spurling GK, Mansfield PR, Montgomery BD, Lexchin J, Doust J, Othman N, et al. Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review. PLoS Med 2010;7:e1000352. http://dx.doi.org/10.1371/journal.pmed.1000352
9. Dean J, Loh E, Coleman JJ. Pharmaceutical industry exposure in our hospitals: the final frontier. Med J Aust 2016;204:20-2. http://dx.doi.org/10.5694/mja15.00734
10. No Advertising Please. 2014. http://noadvertisingplease.org/ [cited 2016 Jul 1]

LETTERS

Letters to the Editor

Menstrual problems in women with intellectual disability

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The article on managing menstrual problems for women and girls with intellectual disability[1] was a very thorough review of the various medical, social and ethical dilemmas faced by clinicians. However, I would like to draw attention to the use of long-acting reversible contraception in these patients.

Insertion of the levonorgestrel-releasing intrauterine device (Mirena) into a uterine cavity less than 6 cm (by ultrasound) may increase the incidence of expulsion, bleeding, pain, perforation, and possibly pregnancy. Its use may therefore be limited in younger patients with intellectual disability.

The use of the medroxyprogesterone injection (Depo-Provera or Depo-Ralovera) appears to be associated with weight gain, particularly in those under 18 years who may already be overweight or obese.[2] Also, its use in women under 20 years has been associated with lower bone density.[3]

The etonorgestrel implant (Implanon) provides reliable contraception and results in amenorrhoea in up to 22% of women. If bleeding patterns are unacceptable, the implant can be used with a low-dose combined oral contraceptive pill or progestogen-only pill if amenorrhoea and long-acting reversible contraception is required and other methods are not preferred.[4,5]

The article discussed the potential for sexual abuse and consent. The perpetrators of sexual abuse may include family members, support workers or co-residents. People with an intellectual disability may not be assertive enough to report the abuse or have the verbal skills to articulate it.[6] Using the etonorgestrel implant which is palpable on the arm may further increase the risk of abuse as the perpetrator is aware of its presence.

I hope other readers will derive benefit and certainly offer better care to their patients with intellectual disability.

Srishti Dutta
General practitioner
Village Family Practice, Samford Village
Warner Family Medical Practice
Brisbane, Qld

REFERENCES

1. Tracy J, Grover S, Macgibbon S. Menstrual issues for women with intellectual disability. Aust Prescr 2016;39:54-7. http://dx.doi.org/10.18773/austprescr.2016.024
2. Faculty of Sexual and Reproductive Healthcare clinical guidance. Progestogen-only injectable contraception. London: Faculty of Sexual and Reproductive Healthcare; 2014. http://www.fsrh.org/documents/cec-ceu-guidance-injectables-dec-2014 [cited 2016 Jul 1]
3. Walsh JS, Eastell R, Peel NFA. Effects of depot medroxyprogesterone acetate on bone density and bone metabolism before and after peak bone mass: a case-control study. J Clin Endocrinol Metab 2008;93:1317-23. http://dx.doi.org/10.1210/jc.2007-2201
4. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Reprod Health Care 2008;13 Suppl 1:13-28. http://dx.doi.org/10.1080/13625180801959931
5. Brache V. Treatment of vaginal bleeding irregularities induced by progestin-only contraceptives: RHL commentary. Geneva: The WHO Reproductive Health Library; 2007. http://apps.who.int/rhl/fertility/contraception/vbcom/en [cited 2016 Jul 1]
6. Eastgate G, Scheermeyer E, van Driel ML, Lennox NG. Intellectual disability, sexuality and sexual abuse prevention: a study of family members and support workers. Aust Fam Physician 2012;41:135-9.

Jane Tracy, one of the authors of the article, comments:

We thank the reader for the valuable comments made and wholeheartedly support their commitment to improving the care of patients with an intellectual disability. Our article was intended to provide an overview of the approach to supporting women to manage their menstruation, rather than focus on the medications because the drug effects are, in general terms, the same for women with and without disability. We agree, however, that the hormonal products discussed can cause irregular bleeding which may cause particular challenges for some women with intellectual disability. For others, they have been liberating when menorrhagia and dysmenorrhoea have previously limited activities and quality of life.

The reader's point about the use of contraceptives increasing the risk of sexual abuse when the perpetrator knows that pregnancy is unlikely to follow is shocking and true, and underlines the vulnerability of these women and girls. It follows that we, as medical practitioners caring for our patients, must be all the more vigilant to the possibility of abuse. Suspicion may be raised by genital symptoms (irritation, lacerations, bruising), infections, or the appearance of new behaviours characterised by fear, avoidance of certain situations or people, or behaviours of a sexual nature.

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

We encourage medical practitioners to review the care of their patients with intellectual disability to ensure optimal physical and mental health, including social, sexual and reproductive health, to optimise opportunity, function and quality of life for all.

ARTICLE

Acute sinusitis and sore throat in primary care

Chris Del Mar
Professor of Public Health
Centre for Research in Evidence-Based Practice
Faculty of Health Sciences and Medicine
Bond University
Gold Coast, Queensland

Keywords
acute sinusitis, antibiotic, sore throat symptom, tonsillitis

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SUMMARY

Sore throat and acute sinusitis are not straightforward diagnoses. Trying to guess the responsible pathogen may not be the best approach.

Being guided by empirical evidence may be more useful. It suggests some, but very few, benefits for antibiotics. This has to be balanced with some, but few, harms from antibiotics, including diarrhoea, rash and thrush.

Prescribers should also be aware of the risk of antibiotic resistance for the individual, as well as for the population as a whole.

GPs should explain the evidence for the benefits and the harms of antibiotics to patients within a shared decision-making framework.

Introduction

Sore throat and acute sinusitis are both common reasons for consultations in Australian primary care. However, deciding how to manage affected patients is far from straightforward.

Diagnosis

Acute respiratory infections involve the respiratory mucosa that lines the pharynx and nasal passages, including sinuses and upper airway. Accurate diagnosis is clouded by a very wide spectrum of different sources of illness, and a vast array of microorganisms that are associated with, and may cause, infection. Many of these bacteria are normally present as commensals. We probably shed different types of virus far more often than we suffer symptoms of a viral infection.

Symptoms can start at any mucosal site and go to any other – sniffles (nose), sore throat (tonsils or pharynx), acute cough (upper airway) and fever or malaise (systemic) – in any order (see Fig.).

Is the infection bacterial or viral?

Because the question of whether an infection is caused by bacteria or a virus underpins the conventional rational approach to management of infections, it has been the focus of much investigation. However, many studies of the microbiological environment of people with infection are difficult to interpret.

One of the organisms of greatest concern is group A beta-haemolytic streptococci. Historically, this infection has resulted in non-suppurative complications (acute rheumatic fever and glomerulonephritis), and secondary infections such as acute otitis media, sinusitis and quinsy. It is notoriously hard to predict from clinical signs,[1] and culturing takes days, leaving only near-patient antigen testing as an option. Moreover, group A beta-haemolytic streptococci together with other organisms that cause respiratory infections (*Neisseria meningitidis*, *Haemophilus*, *Chlamydia* and *Legionella*) exist very commonly in people without symptoms.

Before focusing too closely on diagnosis, it is worth thinking about its purpose. How will treatment be influenced by diagnosis?

Treatment

The natural course of both sore throat and sinusitis is spontaneous resolution. Three questions should be asked:

- Do antibiotics reduce the severity or duration of symptoms?
- Do they reduce any complications?
- Do other interventions relieve symptoms?

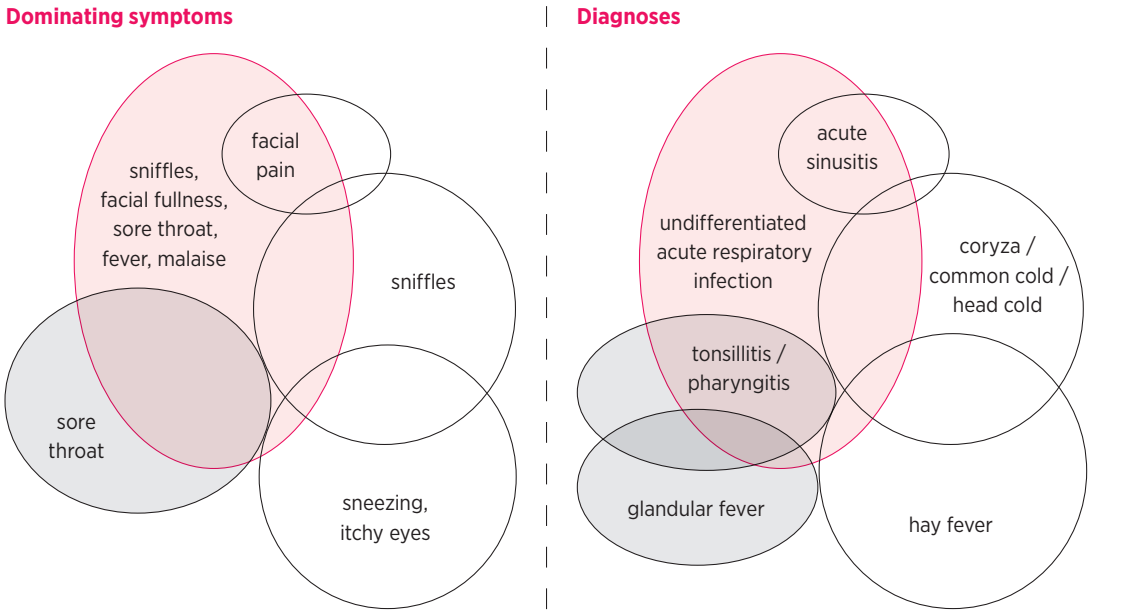
These are necessary questions because of the spectre of antibiotic resistance – something that is approaching a catastrophe.[2]

The evidence: antibiotics for acute sinusitis

In a Cochrane review investigating antibiotics for acute sinusitis, five studies randomised over 1000 patients to antibiotics or placebo.[3] Analysis of the trials found there was a 0.66 risk ratio (95% CI* 0.47–0.94) if antibiotics were used, which

* CI confidence interval

Fig. **Overlapping symptoms and diagnoses of different acute respiratory infections**



means the relative risk of still having the illness at 1–2 weeks was 66% with antibiotics. Nevertheless, 86% of patients given placebo had recovered by 1–2 weeks anyway. This means that six out of every seven patients treated with antibiotics gained no benefit after 1–2 weeks, and by 16 to 60 days there was no difference in recovery and reports of complications between the antibiotic and placebo groups. The diagnostic inclusion criteria for the trials were rigorous with confirmation by X-ray or CT scan, or sinus puncture and aspiration. Clinical diagnosis was also more stringent than in normal clinical practice in Australia. The normal diagnostic spectrum of disease is much wider in general practice than in the trials, so the response to treatment would probably be less.

The evidence: antibiotics for acute sore throat

Another Cochrane review identified 15 trials (including 3621 participants) assessing antibiotics for acute sore throat.[4] These trials reported on the incidence of symptoms three days after the patient had been seen by a clinician. (This is when the greatest benefit of antibiotics is evident.) In the control group, about 77% of patients were still experiencing throat soreness compared with 66% of patients given antibiotics (mostly penicillin). This represents a risk ratio of 0.68 (95% CI 0.59–0.79). The evidence is very robust (even a new well-conducted trial is unlikely to alter the summary effect substantively).[4] The number of patients who need to be treated with antibiotics for one of them to benefit is 3.7 for those who have a positive throat swab for streptococci, 6.5 for those with a negative swab, and 14.4 for those not swabbed. It should be noted that trials that did not swab had a less serious case mix.

So if symptom control is not a good enough reason for using antibiotics, are there other reasons? Historically, sore throat has been of greater concern for its complications than its symptoms. Of these, acute rheumatic fever dominates. It is hard for us to appreciate now, 100 years later, the fear of 'strep throat' that used to frighten parents. An analysis of 16 trials of 10 101 patients found that 10 days of penicillin for sore throat was highly protective against acute rheumatic fever, with a risk ratio of 0.20 (95% CI 0.18–0.44).[4] However, the trials are now more than 50 years old, and acute rheumatic fever has been disappearing steadily since the start of the 1900s. (The discovery of antibiotics in the mid-1900s makes no discernible blip on this downward trend.) Now the risk of acute rheumatic fever is low – one case in every 10 GP-practising lifetimes – and is a weak justification for antibiotic use. In contrast, rural and remote indigenous communities of Australia experience acute rheumatic fever enough for antibiotic use for sore throat to be important.

Harms from antibiotics

Evidence is accumulating that antibiotics deliver common harms, including rashes, diarrhoea and thrush. However, data on adverse drug reactions are not comprehensive.[5] If the infection is serious, these

common adverse reactions can be dismissed as trivial. However, if as in the case of antibiotics for sore throat and acute sinusitis, the benefits are marginal, antibiotic harms need to be factored in. GPs should discuss these harms, balanced against any benefits, with the patient before deciding on management.

Antibiotic resistance

There is also concern about antibiotic resistance. This is obvious for harm at the population level, but there is evidence that individuals carry antibiotic-resistant commensal bacteria for up to 12 months.[6] The extent to which this compromises the effectiveness of antibiotics for subsequent potentially more serious infections has not been quantified.

Alternatives to antibiotics

Currently there are few effective alternatives to antibiotics in primary care. There is surprisingly little empirical evidence for the effectiveness of analgesics, and too little for other over-the-counter products (decongestants, several complementary and alternative medicines, caffeine) to recommend them. Steroids have been shown to be effective for acute sinusitis in four trials of 1943 patients.[7] After 2–3 weeks, sinusitis resolved or improved in 73% of patients using intranasal steroids compared with 66% of those not using them, which means that 14 patients need to be treated for one to benefit.

Bringing this all together when talking to patients

The great challenge is communicating this complexity to patients, who might oversimplify the problem to the fact that there is infection, that it may be caused by bacteria and that antibiotics kill bacteria. A shared decision-making approach enables the clinician to explain the evidence to the patient clearly so they can join in when the health choices are made.[8] When presented with evidence, patients are often surprised to find the benefits modest, with harms of the same effect size, and become less interested in pursuing antibiotics.

Conclusion

Treatment options for sore throat and acute sinusitis are few. However, the illnesses resolve without treatment and, with a few important exceptions, complications are rarely a problem. We probably do patients most good by excluding more sinister illness, and reassuring them that the illness will spontaneously resolve. <

Conflict of interest: Chris Del Mar has received research funding from the National Health and Medical Research Council and the Commonwealth Department of Health.

REFERENCES

1. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ 1998;158:75-83.
2. Department of Health, Department of Agriculture. National Antimicrobial Resistance Strategy 2015-2019. Commonwealth of Australia; 2015. www.health.gov.au/internet/main/publishing.nsf/Content/ohp-amr.htm#tocstrategy [cited 2016 Jul 1]
3. Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, Liira H, Williams JW Jr, Mäkelä M. WITHDRAWN: Antibiotics for acute maxillary sinusitis in adults. Cochrane Database Syst Rev 2015:CD000243.
4. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. Cochrane Database Syst Rev 2013:CD000023.
5. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ 2015;187:E21-31. http://dx.doi.org/10.1503/cmaj.140848.
6. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096. http://dx.doi.org/10.1136/bmj.c2096
7. Zalmanovici Trestioreanu A, Yaphe J. Intranasal steroids for acute sinusitis. Cochrane Database Syst Rev 2013:CD005149.
8. Hoffmann TC, Légaré F, Simmons MB, McNamara K, McCaffery K, Trevena LJ, et al. Shared decision making: what do clinicians need to know and why should they bother? Med J Aust 2014;201:35-9. http://dx.doi.org/10.5694/mja14.00002

FURTHER READING

Antibiotic. Version 15. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2016. www.tg.org.au [cited 2016 Jul 1]

ARTICLE

The management of gout

SUMMARY

Gout is a common inflammatory arthritis that is increasing in prevalence. It is caused by the deposition of urate crystals.

Non-steroidal anti-inflammatory drugs, colchicine and corticosteroids are options for the management of acute gout. They are equally efficacious and comorbidities guide the best choice.

Allopurinol is an effective treatment for reducing concentrations of uric acid. Renal function guides the starting dose of allopurinol and the baseline serum uric acid concentration guides the maintenance dose.

Febuxostat is another xanthine oxidase inhibitor. It is clinically equivalent to allopurinol.

Uricosuric drugs, such as probenecid, increase uric acid excretion. New drugs in this class will soon become available and are likely to have a role in the treatment of patients who do not respond to other drugs.

Andrew Finch
Rheumatology and clinical pharmacology registrar

Paul Kubler
Rheumatologist and clinical pharmacologist
Royal Brisbane and Women's Hospital
Brisbane

Keywords
allopurinol, febuxostat, gout, uric acid

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Introduction

Gout is one of the most common inflammatory arthropathies. Studies suggest a prevalence of 1.7% in Australia and 2.7% in New Zealand, with higher rates in Maori and islander populations.[1] The National Health and Nutrition Examination Survey (NHANES) in the USA and studies in New Zealand, China and the UK have shown that gout and hyperuricaemia are increasing in prevalence.[2,3] A study of its prevalence in Aboriginal Australians in 1965 found an absence of gout, but in 2002, the prevalence had risen to 9.7% in men and 2.9% in women.[4] The prevalence of gout in the USA in 2007–08 was 6%, but the prevalence of hyperuricaemia was 21%.[2,4,5]

Hyperuricaemia is defined as a serum uric acid more than 0.36 mmol/L in women and more than 0.42 mmol/L in men. About 10% of people with hyperuricaemia develop gout, but 80–90% of patients with gout are hyperuricaemic.[4,5] The chance of developing gout increases with increasing serum concentrations of uric acid. Why only a minority of those with hyperuricaemia develop clinical gouty arthritis is unclear.[2] At present, there is insufficient evidence to recommend treatment of asymptomatic hyperuricaemia to prevent gouty arthritis, chronic kidney disease or cardiovascular events.[1]

Despite the high prevalence of gout and the availability of safe and effective therapies, there remains considerable practice variation in diagnosis and management.[1]

Pathophysiology

Gout results from a raised total body uric acid concentration with consequent deposition of crystals in joints and occasionally elsewhere. Unlike most mammals, humans lack the enzyme capable of degrading uric acid. Humans tend to have far higher urate concentrations and these are linked to a constellation of clinical conditions, most notably gout.[6]

There are two important factors that influence uric acid concentrations in the body. These are the amount of uric acid produced and the clearance of uric acid from the body. Approximately two-thirds is removed by renal clearance and one-third by intestinal clearance.

Clinical features

Monosodium urate crystals typically form in relatively cooler parts of the body including the metatarsophalangeal joint of the big toe, the joints of the feet, knees, elbows and hands. The crystals may also deposit in the soft tissues around joints and form tophi which can also occur on the cartilage of the ears.

Gout usually presents as a painful monoarthritis that spontaneously resolves over a few days to one to two weeks. It occurs more commonly in males after puberty, and in females after menopause. Gout is characterised by recurrent flares of severe joint inflammation, but most patients are asymptomatic between attacks.[7]

Diagnosis

For a definitive diagnosis of gout, urate crystals must be demonstrated in synovial fluid or in the tophus.[1] Synovial fluid should be analysed by polarised light microscopy. Once the definitive diagnosis has been made, repeat attacks do not require diagnostic aspiration unless there is a suspicion of joint sepsis. A normal or low serum urate does not exclude the diagnosis of acute gout,[1] because the concentration may not be elevated during an acute attack.

First metatarsophalangeal joint involvement, local erythema, maximal inflammation within 24 hours and hyperuricaemia are suggestive of gouty arthritis, however a response to colchicine and the presence of tophi have a higher diagnostic usefulness.[1] Some imaging modalities such as ultrasound and dual-energy CT scan may be helpful if the diagnosis is uncertain.[1,7]

Several drugs used for treatment of comorbid conditions can alter serum urate concentrations. Losartan, atorvastatin, fenofibrate and calcium channel blockers all have weak urate-lowering properties.[8] Low-dose aspirin and diuretics, particularly thiazide diuretics, increase serum urate. If possible, thiazide diuretics should not be used to treat hypertension in people with gout.

It is important not to overlook other causes of hyperuricaemia. These include renal diseases and myeloproliferative disorders.

Treatment of acute attacks

The management of acute attacks focuses on the prompt treatment of inflammation and pain with the use of anti-inflammatory drugs. Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids are the first-line options, with the choice of drug being influenced by patient comorbidities and concomitant drugs.

Low-dose colchicine has similar efficacy to high-dose colchicine with an adverse-effect profile not significantly different from placebo.[8] The Australian Medicines Handbook recommends 1 mg as soon as possible, then 500 micrograms one hour later (maximum 1.5 mg per course). Do not repeat the course within three days.[9]

Colchicine is a substrate of both cytochrome P450 3A4 and P-glycoprotein so it may interact with antineoplastic drugs, calcium channel blockers (diltiazem and verapamil), calcineurin inhibitors, digoxin, dabigatran, macrolide antibiotics and protease inhibitors.[10]

Short-term NSAIDs (3–5 days) are effective during an acute attack. All drugs in this class have equal efficacy.

Oral prednisolone 35 mg daily has been shown to effectively treat the symptoms of acute gout,[11] however 15–20 mg daily is often recommended.[12] It can usually be stopped after 3–5 days.

Urate-lowering therapy

After management of an acute attack, urate-lowering therapy should be considered in those with gout and at least one of the following:

- tophi
- two or more attacks a year
- chronic kidney disease (stage 2 or worse)
- urolithiasis.[13]

The goals of therapy are to maintain serum uric acid concentrations below a concentration at which urate crystals can form. Preventing the formation of urate crystals reduces the likelihood of joint inflammation, but there is no clear consensus about when to start.

A target serum uric acid of less than 0.30 mmol/L is recommended when tophi are present, otherwise less than 0.36 mmol/L is sufficient.[1] Urate-lowering therapy should be titrated until the target is achieved. Long-term maintenance of the target concentration is recommended. Combination therapy may be required depending on the patient's tolerance and response to therapy. Investigation and treatment of conditions that predispose to gout such as the metabolic syndrome should also be undertaken.

Healthy lifestyle advice should include maintenance of ideal body weight and avoidance of excess alcohol, sugar-sweetened drinks and other known triggers identified for the individual.[1] There is little evidence to support a relationship between a larger consumption of meat and the risk of triggering an attack in those with established gout.[14] Avoidance of some risk factors such as seafood should be weighed against their possible cardiovascular health benefits.[15]

Prophylaxis

When starting urate-lowering therapy, concomitant prophylaxis should be provided for a minimum of six months to prevent flares of gout.[7,8] It is common for flares of gout to occur when starting treatment and when changing the dose. Preventing these flares is a goal of treatment. NSAIDs and low-dose colchicine are first line and low-dose prednisolone is second line.[8]

Colchicine is equal to NSAIDs for long-term prophylaxis, however short-term NSAIDs or oral glucocorticoids may be appropriate depending on the patient's comorbidities and drugs. A dose of 500 microgram (one tablet) of colchicine twice daily for people with normal renal function, and 500 microgram daily in those with renal impairment, may be considered.

Xanthine oxidase inhibitors

Xanthine oxidase catalyses two relevant reactions – the production of hypoxanthine from xanthine and the formation of uric acid from hypoxanthine.[8] The inhibition of xanthine oxidase therefore reduces not only uric acid production but also the production of the uric acid precursor.[8]

Allopurinol

Allopurinol is the first-line drug for urate-lowering therapy. It is a purine analogue which competitively inhibits xanthine oxidase, reducing the production of uric acid.

In patients with normal renal function, allopurinol should be started at a dose of 100 mg daily for the first month. Increase the daily dose by 50 mg every 2–4 weeks until the target serum uric acid concentration is reached. Plasma urate concentrations can be measured monthly during this titration phase and doses higher than 300 mg daily are often required to reach the target.[1] Allopurinol therapy should not be stopped in the event of an acute gout flare and can be safely started during an acute attack.[16,17]

Previously, based on studies published in the 1980s, renal function limited the maximum daily dose of allopurinol.[18] However, basing the dose on creatinine clearance results in only 19% of patients reaching the target serum urate.[8] The final dose of allopurinol needed to reach the target is predicted by the pre-treatment urate concentration, not renal function. Higher doses are required in patients with higher pre-treatment serum urate concentrations.[19]

In patients with renal impairment, allopurinol should be started at a low dose and escalated more slowly than in other patients to achieve the target urate concentration.[1] For example, patients with an estimated glomerular filtration rate less than 30 mL/minute may start at 50 mg every second day. The maximum dose of allopurinol required to reach the target should be determined by tolerability, not renal function.[1]

Adverse effects

Drinking plenty of liquids and eating little and often can help to reduce the most common adverse effects of nausea or vomiting. Less commonly, allopurinol can cause a rash or flaking of the skin. Allopurinol must be ceased and medical advice sought promptly if any rash develops, especially if the very rare adverse effects of mouth ulceration or a severe skin rash develop. Other adverse effects include altered taste, drowsiness and diarrhoea.

A rare but potentially fatal adverse event is allopurinol hypersensitivity syndrome. This is characterised by rashes (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis), eosinophilia, leucocytosis, fever, hepatitis and renal failure. The mortality is reported to be as high as 27%.[20] The mechanisms leading to allopurinol hypersensitivity syndrome are unclear. Risk factors for its development include female sex, age, renal impairment, diuretic use and, in some ethnic groups, the HLA-B*5801 genotype.[20] (People of Asian descent, especially the Han Chinese, have a higher frequency of the HLA-B*5801 allele.[8]) A higher starting dose and quick escalation are associated with an increased risk of developing allopurinol hypersensitivity syndrome. Approximately 90% of cases occur within the first three months of starting treatment.[20] For patients who start allopurinol successfully, there is no association between the maintenance dose and allopurinol hypersensitivity syndrome.[8] This supports the notion of a 'start low and go slow' approach to allopurinol dosing, especially in those with risk factors for hypersensitivity syndrome.

Febuxostat

Febuxostat is a new xanthine oxidase inhibitor but, unlike allopurinol, it is not a purine analogue. It has been effective in a number of trials and is approved in Australia for the treatment of gout in patients who are unable to tolerate allopurinol. Febuxostat is metabolised by the liver and renal excretion is not a major route of elimination. A dose of febuxostat 40 mg per day is clinically equivalent to allopurinol 300 mg in efficacy. If the serum uric acid is greater than 0.36 mmol/L after 2–4 weeks of therapy, febuxostat 80 mg once daily is recommended.

Febuxostat has relatively few drug interactions. It may be safe to use in patients with renal impairment,[2] however the efficacy and safety of febuxostat has not been fully evaluated in patients with a creatinine clearance less than 30mL/minute. Also, there are some concerns about possible cardiovascular events associated with febuxostat and it costs more than allopurinol.[2] Febuxostat is contraindicated in patients with ischaemic heart disease or congestive heart disease and, like allopurinol, is not recommended in patients taking azathioprine or mercaptopurine.

Uricosuric drugs

Uricosurics promote the renal excretion of uric acid and are effective for controlling serum urate. Drugs such as probenecid inhibit organic anion transporters (OATs) in the kidney, which are responsible for the reabsorption of filtered uric acid.[8] Caution is required in those with a history of kidney stones because uricosurics can precipitate uric acid stones.[8] In patients at risk of renal calculi, if no other option is available, increased fluid intake and urinary

alkalinisation may be considered. Probenecid is effective in patients with impaired renal function, contrary to previously held beliefs.[8]

Benzbromarone is a potent uricosuric drug that is available in many countries but not Australia. It is effective as a sole drug in the treatment of gout. When used as add-on therapy in combination with allopurinol, more than 90% of patients reach a serum urate concentration of less than 0.30 mmol/L.[8]

Lesinurad is another uricosuric drug that is currently in clinical trials. It is an inhibitor of uric acid transporters in the renal tubule (urate anion exchanger 1 (URAT1) and organic anion transporter 4 (OAT4)).[8]

Uricases

Uricases (such as rasburicase, a recombinant urate oxidase) metabolise urate to a more soluble form which is then excreted in the urine. They are highly effective at reducing serum urate and treating patients with severe gout,[21] however they are not approved in Australia for this indication. As uricases are proteins, allergic reactions such as rashes, urticaria and bronchospasm are potential complications, especially after repeated infusions.[8,21]

Conclusion

The burden of gout is growing worldwide, due to the increasing number of people with conditions that predispose them to hyperuricaemia such as hypertension, obesity, diabetes, chronic kidney disease and the use of diuretics.[14] Urate-lowering therapy reduces the risk of further attacks of gout, but prophylaxis against flares is required until the maintenance dose is stabilised.

Conflicts of interest: Andrew Finch attended Editorial Executive Committee meetings as the clinical pharmacology registrar for Australian Prescriber *in 2015.*

Conflicts of interest: Paul Kubler was site investigator in multinational Phase III gout studies evaluating lesinurad (Ardea Biosciences, now taken over by AstraZenica). Patient payments went into a public hospital research trust fund (no personal benefit).

Q:

SELF-TEST QUESTIONS

True or false?

1. Allopurinol is not indicated for the treatment of asymptomatic hyperuricaemia.
2. Allopurinol should not be started during an acute attack of gout.

Answers on page 143

REFERENCES

1. Graf SW, Whittle SL, Wechalekar MD, Moi JH, Barrett C, Hill CL, et al. Australian and New Zealand recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion in the 3e Initiative. Int J Rheum Dis 2015;18:341-51. http://dx.doi.org/10.1111/1756-185X.12557
2. Robinson PC, Horsburgh S. Gout: joints and beyond, epidemiology, clinical features, treatment and co-morbidities. Maturitas 2014;78:245-51. http://dx.doi.org/10.1016/j.maturitas.2014.05.001
3. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 2012;125:679-687.e1. http://dx.doi.org/10.1016/j.amjmed.2011.09.033
4. Robinson PC, Taylor WJ, Merriman TR. Systematic review of the prevalence of gout and hyperuricaemia in Australia. Intern Med J 2012;42:997-1007.
5. Smith EU, Díaz-Torné C, Perez-Ruiz F, March LM. Epidemiology of gout: an update. Best Pract Res Clin Rheumatol 2010;24:811-27. http://dx.doi.org/10.1016/j.berh.2010.10.004
6. Galassi FM, Borghi C. A brief history of uric acid: from gout to cardiovascular risk factor. Eur J Intern Med 2015;26:373. http://dx.doi.org/10.1016/j.ejim.2015.04.005
7. Perez-Ruiz F, Dalbeth N, Bardin T. A review of uric acid, crystal deposition disease, and gout. Adv Ther 2015;32:31-41. http://dx.doi.org/10.1007/s12325-014-0175-z
8. Robinson PC, Dalbeth N. Advances in pharmacotherapy for the treatment of gout. Expert Opin Pharmacother 2015;16:533-46. http://dx.doi.org/10.1517/14656566.2015.997213
9. Australian medicines handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2016. https://shop.amh.net.au/products/books/2016 [cited 2016 Jul 1]
10. Finch A, Pillans PI. P-glycoprotein and its role in drug–drug interactions. Aust Prescr 2014;37:137-9. http://dx.doi.org/10.18773/austprescr.2014.050
11. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008;371:1854-60. http://dx.doi.org/10.1016/S0140-6736(08)60799-0
12. eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2016. www.tg.org.au [cited 2016 Jul 1]
13. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al.; American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431-46. http://dx.doi.org/10.1002/acr.21772
14. Lippi G, Mattiuzzi C, Cervellin G. Meat consumption and gout: friend, foe or neither? Rheumatol Int 2015;35:1443-4. http://dx.doi.org/10.1007/s00296-015-3254-9
15. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol 2010;22:165-72. http://dx.doi.org/10.1097/BOR.0b013e328335ef38
16. Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. Am J Med 2012;125:1126-1134.e7. http://dx.doi.org/10.1016/j.amjmed.2012.05.025
17. Turner J, Cooper D. Does colchicine improve pain in an acute gout flare? Ann Emerg Med 2015;66:260-1. http://dx.doi.org/10.1016/j.annemergmed.2015.04.006
18. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 1984;76:47-56. http://dx.doi.org/10.1016/0002-9343(84)90743-5
19. Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum 2012;64:2529-36. http://dx.doi.org/10.1002/art.34488
20. Graham GG, Kannangara DR, Stocker SL, Portek I, Pile KD, Indraratna PL, et al. Understanding the dose-response relationship of allopurinol: predicting the optimal dosage. Br J Clin Pharmacol 2013;76:932-8. http://dx.doi.org/10.1111/bcp.12126
21. Becker MA, Baraf HS, Yood RA, Dillon A, Vázquez-Mellado J, Ottery FD, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. Ann Rheum Dis 2013;72:1469-74. http://dx.doi.org/10.1136/annrheumdis-2012-201795

FURTHER READING

For consumer information regarding both gout and the drugs used to treat gout, visit the Arthritis Australia website: www.arthritisaustralia.com.au

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ARTICLE

Managing behavioural and psychological symptoms in dementia

SUMMARY

Most patients with dementia have some behavioural and psychological symptoms. While aggression and agitation are easily recognised, symptoms such as apathy may be overlooked.

Behavioural and psychological symptoms should be managed without drugs whenever possible. Although there is little evidence to support their use, antipsychotic drugs are often prescribed to people with dementia.

Before prescribing it is important to exclude other causes of altered behaviour, such as pain or infection. Some symptoms may be artefacts of memory loss rather than psychosis.

Patients with dementia who are prescribed antipsychotic drugs have an increased risk of falls, hospitalisation and death. They should be regularly monitored for adverse effects.

If the patient's symptoms resolve with drug treatment, reduce the dose after two or three months. Stop the drug if the symptoms do not return.

Stephen Macfarlane
Head of Clinical Governance
Dementia Centre
Hammond Care
Sydney

Daniel O'Connor
Emeritus professor
Aged Mental Health
Research Unit
Monash University
Melbourne

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Alzheimer's disease, antipsychotic drug therapy, dementia

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Introduction

Behavioural and psychological symptoms are perhaps the commonest complication of dementia syndromes. About 90% of patients display at least one problematic behaviour.[1] The various types of behaviour that can occur are shown in the Figure.

Despite their frequency, certain symptoms are under-recognised, as their occurrence does not necessarily impinge on the provision of care to the person with dementia. Behaviours that are likely to be missed by care staff are those within the depression cluster (see Fig.). This is because few if any externalising behaviours result, despite the distress experienced by the person with dementia. Behaviours that are harder to ignore are aggression, agitation and psychosis.

General practitioners often find themselves under immense pressure to prescribe. The majority of carers within residential aged-care facilities receive minimal training (a Certificate III in Aged Care can be completed in as little as two days per week over 13 weeks), have a significant and stressful workload, and are paid at a level that is not commensurate with the demands of their jobs. Talking to poorly paid and poorly motivated staff about a complex behavioural intervention that must be implemented consistently across three shifts of carers over the seven-day week is often an exercise in frustration for all parties. Carers, when faced with a behaviour of concern, will often look to the treating doctor for a 'quick fix' that is too often reflected in pressure to prescribe.

Management

A number of key principles should guide the management of behavioural and psychological symptoms of dementia. Drugs should only be used when behavioural interventions have failed. They are a treatment of last resort in most cases. Unfortunately, this advice does not seem to be mirrored by prescribing data in Australia. While only about 3% of mental health-related services subsidised by the Medicare Benefits Scheme were provided to those aged 75 and above, over 30% of those within that age group are prescribed psychotropic drugs subsidised by the Pharmaceutical Benefits Scheme (PBS).[2,3]

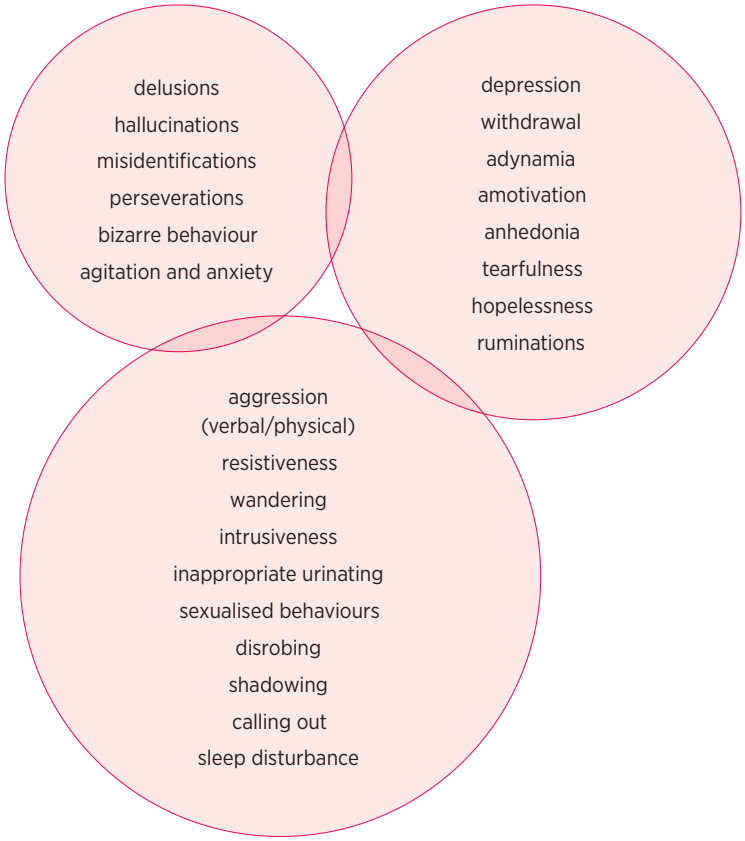
Non-drug interventions

The evidence for the effectiveness of most structured therapies for behavioural and psychological symptoms of dementia is both limited and inconsistent. Methodological difficulties of research in this area have the potential to confound most randomised controlled trials.

A recent meta-analysis failed to support the routine use of reminiscence therapy, simulated presence therapy, validation therapy, acupuncture, aromatherapy or light therapy. There is limited evidence that music therapy, pet therapy and hand massage or touch therapy may have beneficial effects in reducing agitation.[4]

Structured therapies, however, form only a small part of what might be considered non-drug interventions for behavioural and psychological

Fig. **Behavioural and psychological symptom 'clusters' in dementia**



symptoms. Simple techniques such as distraction, redirection, reassurance and reorientation form the core of behavioural interventions that might be applicable in a nursing home setting, and require little other than staff time in order to implement. The choice of intervention should be individualised to the patient and the behaviours that they exhibit, with particular attention being paid to the triggers for each behaviour (e.g. does the problem behaviour only occur at times of nursing intervention, or at particular times of day?). In situations where greater clarity about the role of behavioural interventions might be required, consideration should be given to referral for assessment by local aged psychiatry services or, indeed, to the national Dementia Behaviour Management Advisory Service (DBMAS).

Drug therapy

The Figure shows the variety of symptoms that might be encountered. While a drug might have a PBS indication for treating behavioural disturbances, this does not mean that all symptoms are likely to respond equally well to that drug. There is no drug that will stop people wandering, undressing, urinating inappropriately, shadowing staff or calling out. These are behaviours for which a specific history must be taken in order to elicit and address contributing factors such as pain, infection, and local irritation for which psychotropic drugs have little, if any, role.

Even symptoms such as delusions, which might seem to be suited for drug therapy, can be misleading in cases of dementia. It may be unproductive to think of certain 'delusions' as being truly psychotic in nature. Instead it is better to view certain beliefs as artefacts of poor memory. A prime example would be the 'delusions of theft' reported in approximately 22% of patients with dementia.[5] Other examples could include the failure to correctly identify carers, family members, a spouse, or indeed a patient's own reflection in the mirror.

The general principles of prescribing for older people also apply to patients with behavioural and psychological problems in dementia:

- Target the drug to the symptom. Hallucinations and delusions are likely to be responsive to antipsychotics. For agitation and anxiety the use of an anxiolytic is more appropriate, and persistent insomnia might indicate a short-term role for a hypnotic.
- Start low, go slow with doses.
- Use one drug at a time, at the lowest effective dose. The use of multiple psychotropic drugs should prompt prescribers to consider specialist review or a residential care medication management review.
- Review early, and often, for the emergence of adverse effects. Older people have a greater likelihood of developing extrapyramidal effects, which often emerge during treatment rather than when starting a drug.

Many different classes of drugs have been suggested as treatments for behavioural and psychological symptoms of dementia. There is limited evidence for antipsychotics, antidepressants, benzodiazepines, anticonvulsants, hormonal treatments, cholinesterase inhibitors and memantine. For the most part, this evidence is weak and effect sizes for most drugs are small.[6] In practice, choices are limited within the PBS. Only risperidone, among the atypical antipsychotics, is subsidised for the treatment of psychotic symptoms and aggression. As of July 2015, this approval has become restricted to patients with Alzheimer's dementia, with the approved duration of treatment being limited to 12 weeks.[7]

While the risks of cerebrovascular adverse events associated with antipsychotic drugs in patients

with dementia are now well known, benzodiazepines are not a 'safe' alternative. They pose additional risks from sedation and higher rates of falls, fractures and death.

All prescribers should be aware that placebo response rates are very high for any drug prescribed for behavioural and psychological symptoms of dementia. This may reflect a component of 'treating the staff' by prescribing (anything) within a residential aged-care facility in response to the emergence of a problematic behaviour. Alternatively, the high placebo response rate may reflect the useful aphorism that 'all symptoms in dementia cure themselves with the passage of time'. The natural history is that the symptoms wax and wane according to both environmental factors and factors related to disease progression. There should thus be no reluctance about a trial of deprescribing within 2–3 months of the behaviour settling. If the symptoms do not re-emerge, stop the drug.

Adverse effects

Giving psychotropic drugs to patients with dementia increases the risks of hospitalisation, falls, cerebrovascular adverse events and death. Nursing home patients with dementia who are prescribed antipsychotics are 1.9–2.4 times as likely to have an adverse event that requires hospitalisation, or to die, within 90 days of starting treatment. For patients whose treatment begins in the community the risks are elevated 3.2–3.8 times.[8]

Conclusion

Drugs are an augmentation to behaviour management, not a replacement for it. Regardless of whether a decision to start pharmacotherapy has been made or not, behavioural management strategies should be continued.

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Antipsychotic drugs increase the risk of death in patients with dementia.

4. Drug treatment for behavioural and psychological problems in dementia needs to be continued indefinitely.

Answers on page 143

REFERENCES

1. Colombo M, Vitali S, Cairati M, Vaccaro R, Andreoni G, Guaita A. Behavioral and psychotic symptoms of dementia (BPSD) improvements in a special care unit: a factor analysis. Arch Gerontol Geriatr 2007;44 Suppl 1:113-20. http://dx.doi.org/10.1016/j.archger.2007.01.017
2. Australian Bureau of Statistics. 4329.0 - Characteristics of people using mental health services and prescription medication, 2011. MBS demographics. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4329.0-2011-Main%20Features-People%20accessing%20MBS%20subsidised%20mental%20health-related%20services%20in%202011-2 [cited 2016 Jul 1]
3. Australian Bureau of Statistics. 4329.0 - Characteristics of people using mental health services and prescription medication, 2011. PBS demographics. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4329.0-2011-Main%20Features-People%20accessing%20PBS%20subsidised%20mental%20health-related%20prescription%20medication%20in%202011-3 [cited 2016 Jul 1]
4. O'Neil ME, Freeman M, Christensen V, Telerant R, Addleman A, Kansagara D. A systematic evidence review of non-pharmacological interventions for behavioral symptoms of dementia. Washington DC: Department of Veterans Affairs; 2011.
5. Harvey RJ. Review: delusions in dementia. Age Ageing 1996;25:405-8. http://dx.doi.org/10.1093/ageing/25.5.405
6. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006;14:191-210. http://dx.doi.org/10.1097/01.JGP.0000200589.01396.6d
7. Risperidone and risk of cerebrovascular adverse events in dementia patients. Medicines Safety Update 2015;6:1-2. Canberra: Therapeutic Goods Administration; 2015. http://www.tga.gov.au/publication-issue/medicines-safety-update-volume-6-number-4-august-2015#risperidone [cited 2016 Jul 1]
8. Rochon PA, Normand SL, Gomes T, Gill SS, Anderson GM, Melo M, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008;168:1090-6. http://dx.doi.org/10.1001/archinte.168.10.1090

ARTICLE

Prescribing psychotropic drugs to adults with an intellectual disability

Julian N Trollor
Head[1]

Carmela Salomon
Postdoctoral researcher[1]

Catherine Franklin
Consultant psychiatrist[2]

[1] Department of Developmental Disability Neuropsychiatry School of Psychiatry UNSW Australia Sydney

[2] Queensland Centre for Intellectual and Developmental Disability Mater Research Institute – University of Queensland Brisbane

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antipsychotic drug therapy, genetic syndrome, intellectual disability

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SUMMARY

Mental illness is common in people with intellectual disability. They may also have physical health problems which can affect their mental state.

Difficulties in communication can contribute to mental health problems being overlooked. These may present with changes in behaviour.

Psychological management is usually preferable to prescribing psychotropic drugs. Behavioural approaches are the most appropriate way to manage challenging behaviour.

If a drug is considered, prescribers should complete a thorough diagnostic assessment, exclude physical and environmental contributions to symptoms, and consider medical comorbidities before prescribing. Where possible avoid psychotropics with the highest cardiometabolic burden. Prescribe the minimum effective dose and treatment length, and regularly monitor drug efficacy and adverse effects.

There is insufficient evidence to support the use of psychotropics for challenging behaviour. They should be avoided unless the behaviour is severe and non-responsive to other treatments.

Introduction

The rates of mental illness among people with intellectual disability are at least 2.5 times higher than in the general population.[1] It is a significant concern that this mental illness is often undetected.[2] Challenges include communication difficulties, atypical presentations, coordinating multidisciplinary care, and the paucity of specialist intellectual disability mental health services.

The inappropriate use of psychotropics is common and includes overuse of psychotropic drugs to treat challenging behaviour, excessive dosage and duration of treatment, and polypharmacy. There is often inadequate monitoring of adverse effects.[3-5]

Non-drug management strategies

Psychological and environmental management of mental illness and challenging behaviour is preferable to using psychotropic drugs and in most situations it is indicated as a first- or second-line treatment. The evidence base supporting the use of psychological therapies for mental illness in people with intellectual disability is small but growing. There is growing evidence for the efficacy of cognitive behaviour therapy and mindfulness in the treatment of mood, anxiety disorders and obsessive compulsive disorders. Other psychotherapies, including dialectic behaviour therapy to treat personality disorders, may also be effective in some patients with mild to moderate intellectual disability. However, in cases of profound intellectual disability these approaches may not be practical.[6]

Behavioural approaches are the treatment of choice for the management of challenging behaviour. Applied behaviour analysis and the related concept of positive behaviour support have the best evidence base of all psychosocial approaches for successful management. Applied behaviour analysis conceptualises all behaviour as serving a purpose for the individual and encourages analysis and understanding of the reason for challenging behaviours (and subsequently addressing these reasons) linked with positive reinforcement of adaptive behaviours.[7] These approaches need to be tailored to the individual and implemented by professionals experienced in the area such as specialised behaviour support teams or psychologists with behaviour support training.

The challenge in clinical practice is that access to services is often limited to people with the most severe problems or there may be no service at all. In Australia, some of the current Medicare provisions for access to allied health consultations and medication management reviews are recommended.

Prescribing considerations

If a drug is considered appropriate, the prescribing principles relevant to the general population can

be modified for people with intellectual disability.[1] Additional caution is necessary due to the high number of medical comorbidities, communication barriers, and the complexity of care coordination.[1] The Box summarises key considerations when prescribing psychotropic drugs.

Comorbidity

People with intellectual disability have a significantly elevated incidence of physical health problems.[8] Unrecognised physical illness can result directly in mental illness or indirectly in challenging behaviour. Common problems include epilepsy and disorders causing pain (constipation, gastro-oesophageal reflux disease, musculoskeletal disorders and dental disease). Where possible, physical health problems should be excluded before proceeding to diagnose and treat mental illness or challenging behaviour. If urgent intervention is required, drug use should be reviewed carefully once test results are available. The physical illnesses associated with particular syndromes may also affect the choice of drug (see Table 1). For example, potential interactions with commonly co-prescribed drugs such as anticonvulsants should be considered before prescribing.

The adverse effects of each psychotropic drug should be considered carefully, particularly in people with an elevated risk of cardiometabolic disease. Monitoring in people with intellectual disability requires a holistic and multidisciplinary approach that addresses dietary, lifestyle, socioeconomic, medical

Box Key considerations when prescribing psychotropic drugs to people with intellectual disability

Before prescribing

Determine that prescription is warranted based on:

- confirmed diagnosis of mental illness for which psychotropics are indicated
- challenging behaviour that is severe and non-responsive to maximal cognitive or behavioural therapy
- potential benefits that outweigh the harm
- discussion with carer.

Develop a treatment plan detailing:

- the person's communication needs
- targeted behaviour/symptom, frequency and intensity
- method of measurement of impact of drugs on these behaviours/symptoms including how effects and adverse effects will be assessed
- all previous assessments of medical, psychiatric and functional causes of the behaviour or symptom
- past response to treatment including adverse effects
- a treatment timeline and contingency plan if ineffective.

Obtain consent from the individual or appointed decision maker.

Drug choice

Consider medical comorbidities and potential drug interactions including:

- syndromes that have an increased frequency of cardiometabolic, respiratory disorders or dementia – avoid drugs that will worsen these
- epilepsy – additional epilepsy monitoring may be required when prescribing psychotropics that lower the seizure threshold. Consider also the potential for some anticonvulsants to induce metabolic clearance of co-administered drugs. Doses may need to be adjusted accordingly.

Consider:

- expressed wishes of the person and primary carers
- monitoring requirements of the drug (e.g. blood tests) and whether the person will realistically be able to meet them
- swallowing or absorption impairments
- past response to treatment including adverse effects
- reviewing co-prescribed drugs and taking steps to reduce polypharmacy
- the cardiometabolic 'liability' of the psychotropic drug.

During treatment

Commencing treatment:

- educate the person and their support people about the psychotropic indications for treatment and adverse effects. Communication with formal and informal carers is essential given the central role they often play in monitoring and communicating drug-associated behaviour changes to medical practitioners
- obtain baseline cardiometabolic data
- commence on a low dose and increase gradually.

Monitoring treatment:

- engage the person and their support people in the monitoring process
- set regular review times and a time frame for treatment
- be aware of adverse effects that may be difficult to recognise and report
- watch for behavioural changes after starting treatment or a dose increase as this may indicate adverse effects
- monitor adverse effects on medical comorbidities.

Discontinuing treatment:

- consider discontinuation if treatment is ineffective, there are unacceptable adverse effects, discontinuation is requested, symptoms have resolved or the drug is no longer required
- taper slowly
- avoid simultaneous withdrawal of anticholinergic drugs or multiple psychotropic drugs.

Table 1 **Common medical comorbidities in people with intellectual disability that may alter the choice of psychotropic drug**

Comorbidity	Associated genetic syndromes	Prescription implications
Epilepsy	Down, Fragile X, Angelman, Tuberous sclerosis, Rett, Wolf-Hirschhorn	Exercise caution prescribing psychotropics that lower seizure threshold, e.g. clozapine, tricyclic antidepressants, venlafaxine
Obesity	Down, Turner, Angelman, Prader-Willi	Avoid psychotropics with high cardiometabolic liability as first-line treatment
Dyslipidaemia	Down, Turner, Prader-Willi	Avoid psychotropics with high cardiometabolic liability as first-line treatment
Type 2 diabetes	Down, Turner, Sotos, Prader-Willi	Avoid psychotropics with high cardiometabolic liability as first-line treatment
Hypertension	Turner, Tuberous sclerosis, Williams, Sotos, Prader-Willi	Exercise caution prescribing psychotropics known to raise blood pressure, e.g. venlafaxine, desvenlafaxine, duloxetine
Hypotension	Down	Where possible avoid psychotropics with potential to exacerbate, e.g. chlorpromazine, tricyclic antidepressants, quetiapine
Respiratory difficulties or structural airway abnormalities	Prader-Willi, Down	Where possible avoid highly sedating psychotropics that may exacerbate the risk of respiratory failure
Swallowing difficulties	Cerebral palsy	Exercise caution with psychotropics that exacerbate swallowing difficulties, e.g. clozapine, olanzapine, risperidone, quetiapine
Early onset dementia	Down	Be aware that cognitive adverse effects of some psychotropics may compound cognitive dysfunction in emerging dementia

and genetic risk factors. Potential barriers to effective cardiometabolic monitoring such as communication difficulties and fear of blood tests should be considered when prescribing. Tailored educational materials[9] for people with intellectual disability and for their formal and informal carers are freely available. These include a cardiometabolic monitoring schedule for people with intellectual disability who have been prescribed psychotropic drugs.

Psychiatric diagnosis in severe intellectual disability

Individuals with more severe levels of intellectual disability or communication difficulties may present atypically, for example with non-verbal or behavioural manifestations of psychiatric disorders. If available, assessment and management by specialised intellectual disability mental health services should be considered for people with more complex or severe levels of intellectual disability. Occasionally, with appropriate consents, psychotropic drugs may be tried when mental illness is considered likely, but is hard to verify. In this case, regular review and close monitoring is required and consultation with a specialist is recommended.

Behavioural phenotypes

Advances in genetics have brought a greater understanding of the typical patterns of behaviour and mental illness seen within many genetic syndromes (known as the 'behavioural phenotype').[10] Knowledge of the behavioural phenotype of a syndrome informs the psychiatric assessment and the need to prescribe. For example, people with Down syndrome commonly talk to themselves and this needs to be differentiated from acute psychosis. Lack of recognition of behavioural phenotypes may result in overdiagnosis of mental illness and inappropriate prescribing. Due to the complexities of diagnosis in this area, consultation with specialist intellectual disability mental health services is recommended.

Prescribing for specific mental disorders

The treatment for specific mental disorders is usually the same as in the general population. Table 2 shows some additional points to consider when prescribing psychotropics to people with mental illness and intellectual disability.

Prescribing in autism spectrum disorder

Identification of psychiatric illness in adults with autism spectrum disorder is challenging and often requires specialist input. The incidence of mental illness in autism is higher than in intellectual disability alone[11] and underdiagnosis of mental illness is a risk. Overdiagnosis is also a concern as the core features of autism can mimic mental disorders (especially psychosis, anxiety and obsessive compulsive disorders) and lead to inappropriate prescribing.

Table 2 **Considerations in prescribing for specific mental disorders**

Mental illness	Specific considerations for intellectual disability
Anxiety and associated disorders	Psychological therapies are first-line management. SSRIs are the recommended first-line drugs. Commence on a low dose and increase more slowly than in the general population. Benzodiazepines should only be used short term when required. They may paradoxically heighten agitation, impulsivity or disinhibition.
Depression	SSRIs are most commonly used in intellectual disability. However they have considerable potential for interacting with other drugs. Changes in behaviour (e.g. increased aggression, self-injury, repetitive behaviour) may indicate adverse effects or a manic switch.
Bipolar disorder – acute mania	Lithium and drugs that require regular serum monitoring should only be commenced if regular blood tests are feasible. Adjunctive short-term benzodiazepines may also be required. Prescribe lower doses for people with intellectual disability who are older or who have significant physical comorbidities. ECT may be indicated if initial treatment or subsequent strategies, such as switching psychotropics, are ineffective. Maintenance includes tailored education and supportive psychological strategies.
Schizophrenia and related psychoses	Consider potential sensitivities, monitoring issues and medical comorbidities. Adverse effects may be more likely due to the higher incidence of comorbid conditions (e.g. physical disorders, congenital anomalies). Avoid depot psychotropic administration (greater vulnerability to adverse effects such as tardive dyskinesia). Clozapine may be considered for confirmed cases of treatment-resistant psychosis. Extra precautions include: • the patient's ability to co-operate with blood tests and other monitoring • consideration of medical comorbidities such as epilepsy or elevated baseline cardiometabolic risk profile.

SSRIs selective serotonin reuptake inhibitors

There is emerging evidence that psychological strategies (especially mindfulness and cognitive behaviour therapy) have good efficacy in anxiety and depression in autism. The evidence base for psychotropic prescription for mental illness and challenging behaviour in autism is very limited. Any decision to prescribe psychotropic drugs in adults with autism spectrum disorder therefore requires careful consideration of the harms and benefits.

A Cochrane review[12] found that risperidone had short-term efficacy for irritability, social withdrawal hyperactivity, and stereotypic behaviours in children, with suggested similar benefits in adults with autism spectrum disorder. Although risperidone is listed on the Pharmaceutical Benefits Scheme (PBS) for behaviour disorders due to autism in children, its approval in adults is limited to those who commenced risperidone as a child.

There is also a Cochrane review of aripiprazole in children with autism that reported similar short-term success.[13] However, aripiprazole does not have Therapeutic Goods Administration or PBS approval for autism-related disorders.

Challenging behaviours

Despite the widespread prescribing of psychotropic drugs to treat challenging behaviour in the absence of a defined mental illness,[3] there is little robust evidence to justify this practice.[5,14,15] Reviews of clinical practice suggest that a high level of off-label prescribing occurs and that the atypical antipsychotics are most frequently prescribed, followed by selective serotonin reuptake inhibitors and mood stabilisers.[16] Given the serious cardiometabolic and other adverse effects associated with many psychotropic drugs, all prescriptions for challenging behaviour should be carefully rationalised and should meet the criteria outlined in current consensus guidelines.[17,18]

Where practical, psychotropic prescribing for challenging behaviour should occur under specialist supervision, and only when:

- the challenging behaviour is severe in nature, persistent and places the person or others at risk
- maximal non-pharmacological interventions have already been tried unsuccessfully
- a drug is likely to treat the problem behaviour
- consent for off-label prescription has been obtained, and the person and carers have been informed of any extra financial costs associated with off-label prescription.

Conclusion

Specific evidence for the efficacy of psychotropic drugs in people with intellectual disability and mental illness is lacking. In the absence of a substantial evidence base, clinicians should adapt approaches

applicable to the general population. Treating challenging behaviour with psychotropic drugs is restricted to situations where the behaviour is severe, persistent, risks harm and has not responded adequately to non-pharmacological approaches.

Clinicians should exercise extra vigilance when prescribing and monitoring psychotropic drug therapy given the high rates of medical comorbidities and communication difficulties. Engagement with the carer, family or support staff and careful monitoring of behavioural changes may help to identify emerging adverse effects. Thoughtful prescribing that accounts for diagnoses and underlying medical conditions that may be aggravated by psychotropic drugs may help to minimise adverse effects.

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REFERENCES

1. Trollor JN. Psychiatric disorders: management. In: Management guidelines: developmental disability. Version 3. Melbourne: Therapeutic Guidelines Limited; 2012.
2. Mason J, Scior K. 'Diagnostic overshadowing' amongst clinicians working with people with intellectual disabilities in the UK. J Appl Res Intellect Disabil 2004;17:85-90. http://dx.doi.org/10.1111/j.1360-2322.2004.00184.x
3. Deb S, Kwok H, Bertelli M, Salvador-Carulla L, Bradley E, Torr J, et al.; Guideline Development Group of the WPA Section on Psychiatry of Intellectual Disability. International guide to prescribing psychotropic medication for the management of problem behaviours in adults with intellectual disabilities. World Psychiatry 2009;8:181-6. http://dx.doi.org/10.1002/j.2051-5545.2009.tb00248.x
4. McGillivray JA, McCabe MP. Pharmacological management of challenging behavior of individuals with intellectual disability. Res Dev Disabil 2004;25:523-37. http://dx.doi.org/10.1016/j.ridd.2004.03.001
5. Tyrer P, Cooper SA, Hassiotis A. Drug treatments in people with intellectual disability and challenging behaviour. BMJ 2014;349:g4323. http://dx.doi.org/10.1136/bmj.g4323
6. Management guidelines: developmental disability. Version 3. Melbourne: Therapeutic Guidelines Limited; 2012.
7. Emerson E, Einfeld SL. Challenging behaviour. 3rd ed. Cambridge: University Press; 2011.
8. Cooper SA, Melville C, Morrison J. People with intellectual disabilities. BMJ 2004;329:414-5. http://dx.doi.org/10.1136/bmj.329.7463.414
9. Positive cardiometabolic health for people with intellectual disability. Sydney: Department of Developmental Disability Neuropsychiatry (3DN), UNSW Medicine; 2016. http://3dn.unsw.edu.au/content/positive-cardiometabolic-health-adults-intellectual-disability [cited 2016 Jul 1]
10. O'Brien G. Behavioural phenotypes: causes and clinical implications. Adv Psychiatr Treat 2006;12:338-48. http://dx.doi.org/10.1192/apt.12.5.338
11. Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord 2006;36:863-70. http://dx.doi.org/10.1007/s10803-006-0125-y
12. Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. Cochrane Database Syst Rev 2007:CD005040.
13. Ching H, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2012:CD009043.
14. Tyrer P, Oliver-Africano PC, Ahmed Z, Bouras N, Cooray S, Deb S, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. Lancet 2008;371:57-63. http://dx.doi.org/10.1016/S0140-6736(08)60072-0
15. Brylewski J, Duggan L. Antipsychotic medication for challenging behaviour in people with intellectual disability: a systematic review of randomised controlled trials. Cochrane Database Syst Rev 2007:CD000377.
16. Deb S, Unwin G, Deb T. Characteristics and the trajectory of psychotropic medication use in general and antipsychotics in particular among adults with an intellectual disability who exhibit aggressive behaviour. J Intellect Disabil Res 2015;59:11-25. http://dx.doi.org/10.1111/jir.12119
17. The Section of Psychiatry of Intellectual Disability, World Psychiatric Association Working Group. Problem behaviours in adults with intellectual disability: an international guide for using medication. 2010. http://www.wpanet.org/uploads/Sections/Psychiatry_Intellectual/WPA-SPID-International-Guide.pdf [cited 2016 Jul 1]
18. Deb S, Clarke D, Unwin G. Using medication to manage behaviour problems among adults with a learning disability. Quick reference guide. University of Birmingham. 2006. http://thenadd.org/wp-content/uploads/DATABID%20QRG%20final%20version%2015.01.2007.pdf [cited 2016 Jul 1]

FURTHER READING

Deb S. The role of medication in the management of behaviour problems in people with learning disabilities. Advances in Mental Health and Learning Disabilities 2007;1:26-31. http://dx.doi.org/10.1108/17530180200700017

Unwin GL, Deb S. The use of medication to manage problem behaviours in adults with a learning disability: a national guideline. Advances in Mental Health and Intellectual Disabilities 2010;4;4-11. http://dx.doi.org/10.5042/amhid.2010.0538

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ARTICLE

Rituximab in autoimmune diseases

SUMMARY

Rituximab is a monoclonal antibody that depletes B cells from the circulation. It was originally used to treat lymphoma but is increasingly used for the treatment of autoimmune diseases.

Rituximab was found to be effective in randomised controlled trials for rheumatoid arthritis, granulomatosis with polyangiitis and other antineutrophil cytoplasmic antibody-associated vasculitides. However, evidence of efficacy is very limited for many other autoimmune conditions.

Before starting rituximab, it is important to check the patient's baseline immunoglobulins and immunisation status. Patients should also be screened for latent infections and other contraindications.

Katrina L Randall
Immunologist
Department of Immunology
Canberra Hospital

Senior lecturer
ANU Medical School

Canberra

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Introduction

Rituximab was first developed for the treatment of non-Hodgkin lymphoma, and is also used in chronic lymphocytic leukaemia. It is increasingly being prescribed for the treatment of autoimmune diseases. While we know that rituximab works by removing B lymphocytes from the circulation, exactly how this leads to clinical improvement in many of the conditions that rituximab is used to treat is still to be determined.

Mechanism of action

Rituximab is a chimeric monoclonal antibody that binds to the CD20 surface marker expressed on B cells. This includes precursor B cells (pre-B cells) and mature and memory B cells.[1] Following antibody binding, B cells die by a number of mechanisms including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis.[2] Although the loss of B cells from the circulation is transient (usually for about six months), the duration of depletion can be highly variable among individuals.

Rituximab was developed to remove malignant, clonal B cells expressing CD20 in conditions such as lymphoma. Empirically, it makes sense to use it to remove malignant B-cell clones but how does it work in diseases where the B cells are not malignant?

While rituximab decreases concentrations of antibodies that are pathogenic (or presumed pathogenic), levels of other protective antibodies are maintained, such as those to tetanus toxoid.[1] Rituximab does not reduce plasma cells, which secrete antibodies, because they do not express CD20. Instead, the efficacy of rituximab in autoimmune disease is thought to be due to the decrease in the rate of new plasma cell synthesis (as CD20+ B cells are a required intermediary) or to the disruption of another role of B cells in the immune system, such as the role of B cells as antigen-presenting cells to T cells.

Indications for use

In Australia, rituximab is available on the Pharmaceutical Benefits Scheme (PBS) for a number of different types of non-Hodgkin lymphoma and for CD20+ chronic lymphocytic leukemia. It has been shown to be effective in rheumatoid arthritis[3-5] and is subsidised for severe disease.

Evidence from randomised controlled studies has also shown benefit in granulomatosis with polyangiitis and other antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides.[6-8] This led to the approval of rituximab by the Therapeutic Goods Administration in 2013 for ANCA-associated vasculitis. In January 2016, rituximab was added to the PBS for induction of remission (and for re-induction of remission) for granulomatosis with polyangiitis and microscopic polyangiitis, two forms of ANCA-positive vasculitis.

A six-month survey in Australian hospitals, published in 2013, found more than 300 instances of 'off-label' use of rituximab.[9] It was prescribed in over 50 conditions, including autoimmune conditions listed in the Table.[10-17] For most of these conditions, there is only evidence from case reports and case series. For others, randomised controlled studies failed to show benefit for rituximab, or contradictory case studies exist.[9] Randomised controlled studies of systemic lupus erythematosus failed to show a benefit for rituximab despite promising earlier reports. The addition of rituximab to standard immunosuppressive therapy did not show a difference in the outcomes for non-renal and renal lupus erythematosus[10,11] but this may have been due to problems with study design

Table **Off-label use of rituximab in autoimmune diseases**

Condition	Evidence of benefit (if any)
Systemic lupus erythematosus (non-renal and renal)	Randomised controlled trials failed to show benefit when rituximab was added to standard therapy [10,11]
Antiphospholipid syndrome	Case reports and case series including meta-analysis of case series showed benefit [12]
Blistering diseases of the skin, such as pemphigus and cicatricial pemphigoid	Case reports and case series including meta-analysis of case series showed benefit [13,14]
Neurological diseases such as myasthenia gravis and neuromyelitis optica	Case reports and case series showed benefit [15,16]
Immune thrombocytopenia	Randomised controlled trial failed to show benefit [17] despite promising data from case studies

such as the choice of treatment regimen and study outcome measures. In particular, in the study of lupus nephritis, rituximab reduced the need for rescue medication with cyclophosphamide, despite not showing an overall benefit.[10]

A recent randomised controlled trial in immune thrombocytopenia failed to show a difference between rituximab and placebo in the primary outcome measure, despite promising data from case studies.[17]

Contraindications

Patients with acute or chronic infections should not be treated with rituximab and it is also contraindicated in severe congestive heart failure (New York Heart Association Class IV). Known hypersensitivity to rituximab or other mouse-derived proteins is also a relative contraindication, and rituximab should not be given in pregnancy.[1]

Dosing and administration

The optimal dose of rituximab is poorly defined because of limited studies exploring dose response for many conditions. Rituximab is used in hospitals as it is given as an intravenous infusion, although a subcutaneous formulation is also being evaluated. There are two different intravenous dosing strategies – 375 mg/m^2 weekly for four weeks (lymphoma protocol) and 1000 mg fortnightly (independent of body weight) for two doses (rheumatoid arthritis protocol). For some conditions and in some hospitals, the fortnightly strategy is modified to a low-dose strategy which involves two 500 mg doses given 1–2 weeks apart.[18]

Infusion-related reactions to rituximab are common (30% with the first infusion). Premedication with paracetamol and corticosteroid (usually 100 mg of hydrocortisone) is used to minimise these.[1]

Treatment-related infections

As with other immunosuppressants, the main concern with rituximab is infection. While studies have shown that antibodies to vaccine-preventable diseases, such as tetanus, remain normal after treatment, repeated courses of rituximab can be associated with hypogammaglobulinaemia (particularly decreases in total IgG).[19,20] Some studies have shown no increase in infection in patients with rheumatoid arthritis treated with rituximab compared to placebo.[1] A German analysis of data from patients treated with rituximab for autoimmune diseases (excluding rheumatoid arthritis) estimated the rate of serious infections to be 5.3/100 patient years. However as this is registry data, we do not know the rate of serious infection in the 'normal population' or in patients with autoimmune disease not treated with rituximab.[21] Patients with low concentrations of IgG before commencing rituximab are at particular risk of infection due to previous immunosuppression or to the underlying condition for which they are being treated.[22] Risk may also depend on past and current immunosuppression, in particular corticosteroid treatment. Neutropenia has also been described 3–6 months after treatment with rituximab at a rate of 1.5/100 patient years and can be associated with serious infection.[23]

It is important to treat suspected infections early. If the infection is serious, resistant to treatment or recurrent, check full blood counts (including neutrophils) and IgG concentrations and contact the patient's specialist for advice.

There are three particular infections of concern with rituximab – progressive multifocal leucoencephalopathy, hepatitis B and *Pneumocystis jirovecii* pneumonia. Patient information about the risks associated with rituximab is available at http://rheumatology.org.au.

Progressive multifocal leucoencephalopathy

In day-to-day practice, the infection that concerns patients the most is the risk of progressive multifocal leucoencephalopathy. This is caused by reactivation of JC virus and can lead to severe disability or death. It is estimated that there is less than a 1:20 000 chance of developing progressive multifocal leucoencephalopathy when rituximab is used for the treatment of rheumatoid arthritis.[1] There is a slightly higher risk for patients with systemic lupus erythematosus, but this may be confounded by the fact that these patients can develop progressive multifocal leucoencephalopathy independently of rituximab treatment.[24]

Patients, GPs and treating physicians need to investigate and exclude progressive multifocal

leucoencephalopathy for any new or worsening neurological symptoms, particularly visual disturbance, ataxia, confusion and abnormal gait.

Hepatitis B virus

There are reports of the reactivation of hepatitis B virus after treatment with rituximab. A study of these case reports relating to rituximab for lymphoma found an overall mortality rate of 80% from hepatitis B reactivation.[25] However, this high rate could have been due to publication bias. It is important to check hepatitis B serology (including hepatitis B core antibody) in all patients before starting rituximab treatment. For those with positive serology indicating a past or chronic infection, discuss antiviral prophylactic treatment with a specialist.

Pneumocystis jirovecii *pneumonia*

Another infection of concern with rituximab is *Pneumocystis jirovecii* pneumonia.[26] This is an opportunistic infection usually associated with low CD4 T-cell counts. Prophylaxis is generally started when CD4 counts are less than 200 cells/microlitre of blood. However, infections have been described in patients, after rituximab, with CD4 counts greater than 200/microlitre,[26] indicating that this threshold may not be valid in the absence of B cells. The mechanism of susceptibility after the use of rituximab is not known, but may be due to decreased B-cell help for T cells.

The exact incidence of infection in patients with autoimmune disease treated with rituximab is unknown. Rates of 1.5–6% have been reported when rituximab is used for the treatment of lymphoma.[27] Infection is most commonly described when rituximab is used together with other medicines but has also been described with rituximab on its own.[26] Primary prophylaxis with trimethoprim/sulfamethoxazole may therefore be considered when prescribing rituximab.

Immunisation

As immunisation responses are compromised after treatment with rituximab,[28] it is recommended that any required immunisations are given before treatment.[1] Current guidelines recommend pneumococcus and influenza vaccination for patients with autoimmune disease, and hepatitis A and B vaccinations in at-risk groups.[29] A four-week gap between vaccination with non-live vaccines and commencement of rituximab is recommended, but the optimal interval is an area of ongoing research.[1]

Live vaccines are contraindicated in those who have had treatment with rituximab or are being considered for it.

As it is assumed that a protective response to tetanus toxoid booster vaccination may not occur after rituximab treatment, for a tetanus-prone wound, passive immunisation with tetanus antibodies is advised for 24 weeks after rituximab treatment.[29] However if the patient is persistently B-cell lymphopenic, passive immunisation may need to be considered even after this time.

Monitoring and re-treatment

Patients are usually found to have depleted B cells after one dose of rituximab. This is confirmed by checking B- and T-cell lymphocyte subsets through a different surface marker – CD19 – to ensure that rituximab is not just blocking access to the surface marker for the detection antibody. Most clinicians would also follow the titre of the pathogenic (or presumed pathogenic) antibody specific for the disease that is being treated.

The optimum timing and safety and efficacy of any re-treatment with rituximab is still an area of active research.[1] This is reflected in current variable practices, which include patients starting re-treatment:

- when their B cells return before any disease manifestations
- after B cells return and symptoms develop
- after a certain number of months even if there are no detectable B cells in the blood.

Conclusion

Rituximab is being used more widely for the treatment of autoimmune diseases, in many cases as an off-label drug. It works by transiently depleting B cells from the circulation. While it is used increasingly for autoimmune disease, with case studies and case series describing efficacy, for most conditions there have been no randomised controlled studies. Patients need to be appropriately screened before the use of rituximab, and monitored for adverse effects, particularly infection. ◀

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REFERENCES

1. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T, et al.; Rituximab Consensus Expert Committee. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:909-20. http://dx.doi.org/10.1136/ard.2010.144998
2. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. Oncogene 2003;22:7359-68. http://dx.doi.org/10.1038/sj.onc.1206939

3. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al.; REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-806. http://dx.doi.org/10.1002/art.22025
4. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al.; DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390-400. http://dx.doi.org/10.1002/art.21778
5. Peterfy C, Emery P, Tak PP, Ostergaard M, DiCarlo J, Otsa K, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis 2016;75:170-7. http://dx.doi.org/10.1136/annrheumdis-2014-206015.
6. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al.; RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32. http://dx.doi.org/10.1056/NEJMoa0909905
7. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al.; European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20. http://dx.doi.org/10.1056/NEJMoa0909169
8. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. Cochrane Database Syst Rev 2015:CD003232.
9. O'Connor K, Liddle C. Prospective data collection of off-label use of rituximab in Australian public hospitals. Intern Med J 2013;43:863-70. http://dx.doi.org/10.1111/imj.12206
10. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al.; LUNAR Investigator Group. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215-26. http://dx.doi.org/10.1002/art.34359
11. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222-33. http://dx.doi.org/10.1002/art.27233
12. Erkan D, Aguiar CL, Andrade D, Cohen H, Cuadrado MJ, Danowski A, et al. 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. Autoimmun Rev 2014;13:685-96. http://dx.doi.org/10.1016/j.autrev.2014.01.053
13. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, Caux F, Pascal F, Doan S, et al. Rituximab for patients with refractory mucous membrane pemphigoid. Arch Dermatol 2011;147:843-9. http://dx.doi.org/10.1001/archdermatol.2011.54
14. Wang HH, Liu CW, Li YC, Huang YC. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. Acta Derm Venereol 2015;95:928-32. http://dx.doi.org/10.2340/00015555-2116
15. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. J Neurol 2015;262:1115-9. http://dx.doi.org/10.1007/s00415-014-7532-3
16. Collongues N, Brassat D, Maillart E, Labauge P, Ouallet JC, Carra-Dalliere C, et al.; OFSEP and CFSEP. Efficacy of rituximab in refractory neuromyelitis optica. Mult Scler 2016;22:955-9. http://dx.doi.org/10.1177/1352458515602337
17. Ghanima W, Khelif A, Waage A, Michel M, Tjønnfjord GE, Romdhan NB, et al.; RITP study group. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2015;385:1653-61. http://dx.doi.org/10.1016/S0140-6736(14)61495-1
18. Chay J, Donovan P, Cummins L, Kubler P, Pillans P. Experience with low-dose rituximab in off-label indications at two tertiary hospitals. Intern Med J 2013;43:871-82. http://dx.doi.org/10.1111/imj.12207
19. Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum 2007;56:3896-908. http://dx.doi.org/10.1002/art.23059
20. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60-5. http://dx.doi.org/10.1016/j.jaut.2014.11.009
21. Tony HP, Burmester G, Schulze-Koops H, Grunke M, Henes J, Kötter I, et al.; GRAID investigators. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis Res Ther 2011;13:R75. http://dx.doi.org/10.1186/ar3337
22. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al.; AutoImmunity and Rituximab registry and French Society of Rheumatology. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 2010;62:2625-32. http://dx.doi.org/10.1002/art.27555
23. Salmon JH, Cacoub P, Combe B, Sibilia J, Pallot-Prades B, Fain O, et al. Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the AutoImmunity and Rituximab registry. RMD Open 2015;1:e000034. http://dx.doi.org/10.1136/rmdopen-2014-000034
24. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy in patients with rheumatic diseases: are patients with systemic lupus erythematosus at particular risk? Autoimmun Rev 2008;8:144-6. http://dx.doi.org/10.1016/j.autrev.2008.07.006
25. Hoofnagle JH. Reactivation of hepatitis B. Hepatology 2009;49 Suppl S5:S156-65. http://dx.doi.org/10.1002/hep.22945
26. Martin-Garrido I, Carmona EM, Specks U, Limper AH. Pneumocystis pneumonia in patients treated with rituximab. Chest 2013;144:258-65. http://dx.doi.org/10.1378/chest.12-0477
27. Jiang XQ, Fang L, Mei XD, Wang XJ, Bao MH. Pneumocystis jiroveci pneumonia in patients with non-Hodgkin's lymphoma after Rituximab-containing regimen: two cases of report and literature review. J Thorac Dis 2013;5:E162-6. http://dx.doi.org/10.3978/j.issn.2072-1439.2013.08.35
28. Eisenberg RA, Jawad AF, Boyer J, Maurer K, McDonald K, Prak ET, et al. Rituximab-treated patients have a poor response to influenza vaccination. J Clin Immunol 2013;33:388-96. http://dx.doi.org/10.1007/s10875-012-9813-x
29. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70:414-22. http://dx.doi.org/10.1136/ard.2010.137216

Top 10 drugs

Aust Prescr 2016;39:135
http://dx.doi.org/10.18773/austprescr.2016.055

Tables 1–3 show the top 10 subsidised drugs for the year July 2014 – June 2015. The figures are based on PBS and RPBS prescriptions from the date of supply, and do not include private prescriptions or prescriptions under the co-payment.

Table 1 **Top 10 drugs by DDD/1000 pop/day** *

Drug		DDD/1000 pop/day
1.	atorvastatin	54.65
2.	rosuvastatin	39.47
3.	paracetamol	34.14
4.	perindopril	33.80
5.	amlodipine	30.08
6.	irbesartan	27.33
7.	esomeprazole	25.27
8.	candesartan	23.41
9.	ramipril	21.62
10.	telmisartan	18.84

Table 2 **Top 10 drugs by prescription counts**

Drug		Prescriptions
1.	atorvastatin	7 787 189
2.	esomeprazole	7 170 908
3.	rosuvastatin	7 070 240
4.	paracetamol	6 446 680
5.	pantoprazole	4 489 551
6.	perindopril	4 015 432
7.	metformin	3 589 937
8.	fluticasone and salmeterol	3 147 115
9.	irbesartan	2 992 442
10.	salbutamol	2 976 106

Table 3 **Top 10 drugs by cost to government**

Drug		Cost to government (A$)	DDD/1000 pop/day *	Prescriptions
1.	adalimumab	311 616 305	0.57	176 062
2.	rosuvastatin	206 589 091	39.47	7 070 240
3.	aflibercept	192 839 767	†	123 123
4.	ranibizumab	179 612 417	†	116 311
5.	fluticasone and salmeterol	175 215 964	†	3 147 115
6.	esomeprazole	174 179 985	25.27	7 170 908
7.	etanercept	164 075 133	0.31	93 629
8.	rituximab	156 563 805	†	46 763
9.	insulin glargine	142 760 966	7.45	347 652
10.	fingolimod	134 752 870	0.19	58 858

* DDD/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day. DDD includes use in combination products. The calcuation is based on ABS 3101.0 – Australian Demographic Statistics for June 2014 (as at December 2014).

† The World Health Organization has not allocated a DDD for this drug.

DDD defined daily dose, PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Department of Health, 15 June 2016. © Commonwealth of Australia

FEATURE

Medicinal mishap

Trimethoprim-induced critical hyperkalaemia

Alice Kennard
Advanced trainee in renal medicine

Darren M Roberts
Nephrologist and Clinical pharmacologist
Canberra Hospital and Community Services
Canberra

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Case

An 88-year-old woman presented for investigation of generalised weakness, collapse, bradycardia and delirium. She had a history of recurrent urinary tract infections and had started trimethoprim five days previously. Her past medical history included hypertension, paroxysmal atrial fibrillation with cerebrovascular accident and stage 4 chronic kidney disease attributed to reflux nephropathy and renovascular disease. Her usual drugs were quinapril, doxepin, atorvastatin, frusemide, nebivolol, pregabalin, hexamine hippurate and warfarin.

On admission the patient's serum potassium was 7.9 mmol/L with acute kidney injury (serum creatinine 300 micromol/L, usual baseline 120 micromol/L). Her ECG showed atrial fibrillation with a ventricular rate of 50 beats/minute.

The hyperkalaemia was managed with intravenous sodium bicarbonate, insulin and glucose plus oral sodium polystyrene sulfonate. There was continuous cardiac monitoring. The trimethoprim was ceased and quinapril, frusemide, pregabalin, nebivolol and doxepin were withheld due to the potential for them to contribute to her overall condition. The patient's symptoms, signs and biochemistry stabilised over five days and she was discharged home.

At a subsequent review her quinapril was stopped. She was advised to avoid trimethoprim because of the risk of precipitating hyperkalaemia.

Four months later the woman developed another urinary tract infection but she was again given trimethoprim. Within six days she was readmitted with critical hyperkalaemia (serum potassium 8.1 mmol/L) associated with acute kidney injury (creatinine 200 micromol/L), bradycardia, lethargy and shortness of breath. She required haemodialysis in the intensive care unit, but made a favourable recovery.

The Naranjo score[1] for predicting adverse drug reactions was 7 in this patient. This means that the hyperkalaemia was a probable adverse reaction to trimethoprim.

Comment

There were several other possible causes for the hyperkalaemia in the initial presentation. These include acute kidney injury, chronic kidney disease and treatment with quinapril. Although hyperkalaemia is associated with weakness and bradycardia, the patient was taking other drugs that may have contributed to these symptoms, notably nebivolol, doxepin and pregabalin. However, on her second presentation the patient had not been taking quinapril.

Hyperkalaemia is now a well-recognised adverse reaction to trimethoprim, however this was not reported until approximately 25 years after the antibiotic was first marketed. Detailed human and animal studies in the 1990s found that trimethoprim interferes with potassium excretion by antagonising the epithelial sodium channel in the distal tubule. This results in an effect like that of the potassium-sparing diuretic amiloride.[2] In addition, trimethoprim antagonises the renal tubular secretion of creatinine, causing an increase in serum creatinine concentration which can be interpreted as acute kidney injury – however, there is no change in glomerular filtration rate.[3]

The Australian Medicines Handbook[4] warns of the risk of hyperkalaemia from trimethoprim in patients with chronic kidney disease and in those taking other drugs that cause potassium retention. It recommends against using trimethoprim in severe renal impairment.

Canadian case-control studies investigated sudden deaths in older outpatients (>66 years old) prescribed antibiotics. Compared to amoxycillin there was an adjusted odds ratio of 1.38 (95% CI* 1.09–1.76) for sudden death in patients prescribed trimethoprim with a renin-angiotensin system inhibitor. The adjusted odds ratio was 2.46 (95% CI 1.55–3.90) in those prescribed trimethoprim and spironolactone (approximately 50% were also prescribed a renin-angiotensin system inhibitor).[5] These deaths were thought to relate to unrecognised critical hyperkalaemia. In another study, co-prescribing of trimethoprim with a renin-angiotensin system inhibitor was associated with an adjusted odds ratio of 6.7 (95% CI 4.5–10.0) for hyperkalaemia-associated hospitalisation, compared to those co-prescribed amoxycillin.[6]

* CI confidence interval

Recommendation

Trimethoprim is a well-recognised cause of hyperkalaemia, particularly in older patients, those with renal impairment or those taking a renin-angiotensin system inhibitor or spironolactone. When possible, alternative antibiotics should be prescribed to susceptible patients. If these patients are prescribed trimethoprim, monitoring of serum potassium is recommended.

Conflict of interest: Darren Roberts is a member of the Australian Prescriber *Editorial Executive Committee.*

REFERENCES

1. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45. http://dx.doi.org/10.1038/clpt.1981.154
2. Choi MJ, Fernandez PC, Patnaik A, Coupaye-Gerard B, D'Andrea D, Szerlip H, et al. Brief report: trimethoprim-induced hyperkalemia in a patient with AIDS. N Engl J Med 1993;328:703-6. http://dx.doi.org/10.1056/NEJM199303113281006
3. Naderer O, Nafziger AN, Bertino JS Jr. Effects of moderate-dose versus high-dose trimethoprim on serum creatinine and creatinine clearance and adverse reactions. Antimicrob Agents Chemother 1997;41:2466-70.
4. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2016.
5. Antoniou T, Hollands S, Macdonald EM, Gomes T, Mamdani MM, Juurlink DN; Canadian Drug Safety and Effectiveness Research Network. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. CMAJ 2015;187:E138-43. http://dx.doi.org/10.1503/cmaj.140816
6. Antoniou T, Gomes T, Juurlink DN, Loutfy MR, Glazier RH, Mamdani MM. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. Arch Intern Med 2010;170:1045-9. http://dx.doi.org/10.1001/archinternmed.2010.142

NEW DRUGS

New drugs

Nivolumab

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First published online 20 May 2016

Approved indications: melanoma, non-small cell lung cancer

Opdivo (Bristol-Myers Squibb)
vials containing 10 mg/mL as concentrate
Australian Medicines Handbook section 14.2

The immune system contains checkpoints which attenuate the immune response to prevent damage to normal cells. However, the checkpoint pathways may limit the immune response to cancer cells. One of the receptors involved in this immunosuppression is programmed death 1 (PD-1). Ligands of PD-1 produced by certain cancers bind to the PD-1 receptor on T-lymphocytes, inhibiting the ability of the T cells to attack the tumour cells.

Nivolumab is a monoclonal antibody which binds to the PD-1 receptor. This stops the ligands binding to the receptor. By blocking their inhibitory effects on T cells, nivolumab should enhance the immune response to tumours. An initial study in a small number of patients reported tumour responses in colorectal cancer, renal cell carcinoma, non-small cell lung cancer and melanoma.[1]

Melanoma

Existing targeted therapies for advanced malignant melanoma include the BRAF and MEK inhibitors for patients with the BRAF mutation, and the CTLA-4 immune checkpoint inhibitor ipilimumab.[2] There have now been several trials of nivolumab in stage III and IV melanoma.

Monotherapy

In a trial of patients without a BRAF mutation 210 were randomised to receive infusions of nivolumab every two weeks and 208 were randomised to receive infusions of the alkylating agent dacarbazine every three weeks. If tolerated, the treatment continued until the cancer progressed. The median progression-free survival was 5.1 months with nivolumab and 2.2 months with dacarbazine. At one year, the overall survival rate was 72.9% for nivolumab and 42.1% for dacarbazine.[3]

An open-label trial studied monotherapy in patients with advanced melanoma which had progressed despite treatment with ipilimumab. While 272 patients were randomly allocated to infusions of nivolumab, the treating clinicians chose a chemotherapy regimen, such as dacarbazine, for a further 133 patients. An interim analysis of the first 120 patients given nivolumab, with a minimum follow-up of six months, found a greater radiological response. There was a response in 38 (31.7%) of these patients compared with a response in 5 (10.6%) of 47 patients given chemotherapy. Responses were seen in patients with or without the BRAF mutation.[4]

Combination therapy

As nivolumab and ipilimumab have different sites of action they have been studied as a combination treatment for melanoma. One trial randomised 316 patients to nivolumab, 315 to ipilimumab and 314 to both drugs. They were treated until the disease progressed or toxicity became unacceptable. The median progression-free survival was 6.9 months with nivolumab, 2.9 months with ipilimumab and 11.5 months with the combination.[5]

Another trial compared the response rates of the combination to ipilimumab alone in patients whose BRAF mutation status was known. After a minimum follow-up of 11 months, in patients with wild-type tumours, there was a median decrease of 68.1% in tumour volume in the combination group compared with a 5.5% increase in the ipilimumab group. Irrespective of mutation status there was a complete response in 21 (22%) of the 95 patients treated with the combination. None of the 47 patients treated with ipilimumab alone had a complete response. Analysis by mutation status showed that the overall response rate to the combination was 61% (44/72) for patients with wild-type tumours and 52% (12/23) for those with the V600 mutation.[6]

Non-small cell lung cancer

Patients with non-small cell lung cancer have a poor prognosis, especially those with advanced disease which has progressed despite chemotherapy. They usually die within a year. Preliminary investigation found that in previously treated patients given nivolumab 3 mg/kg every two weeks the median overall survival was 14.9 months.[7] This dose was investigated in patients with stage IIIB or stage IV cancer who had previously been treated with platinum-based chemotherapy.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Squamous cell carcinoma

An open-label trial randomised 137 patients to intravenous docetaxel, every three weeks, and 135 patients to nivolumab. The median number of doses given was three for docetaxel and eight for nivolumab. There was a median progression-free survival of 2.8 months with docetaxel and 3.5 months with nivolumab. The median overall survival was 6 months with docetaxel and 9.2 months with nivolumab. At one year, 42% of the nivolumab group were still alive compared with 24% of the docetaxel group.[8]

Non-squamous non-small cell carcinoma

In another open-label trial, 582 patients were randomised to the same regimens of docetaxel or nivolumab. A median of four doses of docetaxel and six doses of nivolumab were infused. Although the median progression-free survival was shorter with nivolumab (2.3 vs 4.2 months), the median overall survival was longer than with docetaxel (12.2 vs 9.4 months). At one year 51% of the nivolumab group and 39% of the docetaxel group were still alive.[9]

Safety

Some of the hazards of intravenously infusing a monoclonal antibody such as nivolumab are predictable. There can be infusion reactions and a wide range of potentially life-threatening immune-related problems. These include pneumonitis, colitis, hepatitis, nephritis and endocrinopathies. Corticosteroids may be required. Treatment with nivolumab may need to be modified or stopped if the patient develops problems such as diarrhoea, rashes or alterations in liver, renal or thyroid function. Common adverse events during the trials were fatigue, nausea, musculoskeletal pain, rash, pruritus and diarrhoea. Nivolumab can also reduce haemoglobin and blood counts. Adverse reactions are likely to be more frequent if nivolumab is given with ipilimumab. The toxicity of this combination resulted in 45% of the patients receiving it for untreated melanoma discontinuing therapy.[6]

Pharmacokinetics

The nivolumab concentrate is diluted and then infused over an hour. Infusions of nivolumab and ipilimumab should not be given at the same time. It is expected that nivolumab will be broken down like other antibodies. Nivolumab has a half-life of about 27 days. Clearance is not affected by mild hepatic or mild–moderate renal impairment. It will be increased if anti-nivolumab antibodies develop.

Conclusion

The trials have shown that nivolumab improves the survival of patients with advanced melanoma and non-small cell lung cancer by a few months (see Table). Other indications are likely to be added. The best use of nivolumab requires further study. For example, how does its effectiveness compare with that of chemotherapy for non-small cell lung cancer? If it is used at earlier stages of treatment, long-term adverse effects may emerge.

Table **Efficacy of nivolumab monotherapy**

Cancer	Treatment	Number of patients	Median progression-free survival (months)	Median overall survival (months)
Previously untreated metastatic melanoma[3]	nivolumab	210	5.1	Not reached‡
	dacarbazine	208	2.2	10.8
Previously untreated advanced melanoma[5]	nivolumab	316	6.9	–
	ipilimumab	315	2.9	–
Previously treated advanced melanoma[4]	nivolumab	272	4.7§	–
	chemotherapy	133	4.2§	–
Advanced squamous cell non-small cell lung cancer[8]	nivolumab	135	3.5	9.2
	docetaxel	137	2.8	6.0
Advanced non-squamous non-small cell lung cancer[9]	nivolumab	292	2.3	12.2
	docetaxel	290	4.2	9.4

‡ after a median follow-up of 8.9 months
§ analysis based on the first 120 patients given nivolumab (47 given chemotherapy)

NEW DRUGS

Nivolumab is not the first antibody aimed at the PD-1 receptor, as pembrolizumab was marketed in Australia during 2015.[10] Although pembrolizumab requires shorter and less frequent infusions, its efficacy and safety have not been directly compared with nivolumab.

T manufacturer provided the product information

REFERENCES *†

1. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75. http://dx.doi.org/10.1200/JCO.2009.26.7609
2. Atkinson V. Medical management of malignant melanoma. Aust Prescr 2015;38:74-8. http://dx.doi.org/10.18773/austprescr.2015.028
3. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320-30. http://dx.doi.org/10.1056/NEJMoa1412082
4. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375-84. http://dx.doi.org/10.1016/S1470-2045(15)70076-8
5. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34. http://dx.doi.org/10.1056/NEJMoa1504030
6. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006-17. http://dx.doi.org/10.1056/NEJMoa1414428
7. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015;33:2004-12. http://dx.doi.org/10.1200/JCO.2014.58.3708
8. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123-35. http://dx.doi.org/10.1056/NEJMoa1504627
9. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-39. http://dx.doi.org/10.1056/NEJMoa1507643
10. Pembrolizumab. Aust Prescr 2015;38:180-2. http://dx.doi.org/10.18873/austprescr.2015.066

Paritaprevir/ritonavir/ombitasvir plus dasabuvir

Viekira Pak (AbbVie)
75 mg/50 mg/12.5 mg tablet plus 250 mg tablet

Paritaprevir/ritonavir/ombitasvir plus dasabuvir with ribavirin

Viekira Pak-RBV (AbbVie)
75 mg/50 mg/12.5 mg tablet plus 250 mg tablet with 200 mg tablet
75 mg/50 mg/12.5 mg tablet plus 250 mg tablet with 600 mg tablet

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Approved indication: chronic hepatitis C
Australian Medicines Handbook section 5.5

The management of hepatitis C is rapidly changing with a move away from regimens containing interferon.[1] This new product contains four antiviral drugs, three of which are combined in one tablet. The product can also be packaged with ribavirin, so some patients will be treated with five drugs simultaneously.

Paritaprevir is a protease inhibitor aimed at the NS3/4A protease, which is essential for viral replication. Its plasma concentration is increased by combining it with ritonavir as this inhibits the metabolism of paritaprevir by cytochrome P450 3A4. Although ritonavir is an antiviral drug, it has no effect on the hepatitis C virus.

Ombitasvir acts on the NS5A protein which is also involved in viral replication. Dasabuvir is a non-nucleoside inhibitor of viral RNA polymerase. Ribavirin is a nucleoside analogue, but its mechanism of action against the hepatitis C virus is uncertain.

Two combined tablets of paritaprevir, ritonavir and ombitasvir are taken once a day while dasabuvir and ribavirin are taken twice a day. All these tablets should be taken with food. The four drugs are contraindicated in patients with severe hepatic impairment and their safety in patients with moderate impairment is unknown. No dose adjustment is recommended in renal impairment, but this would limit the use of ribavirin. The four- or five-drug regimen has the potential to interact with many other drugs including erythromycin, dabigatran, calcium channel blockers, frusemide, proton pump inhibitors and triazolam. There is a long list of contraindicated drugs which includes contraceptives containing ethinyloestradiol, simvastatin, salmeterol, antiepileptic drugs and St John's wort. As ribavirin is teratogenic it is contraindicated in pregnant women and men with pregnant partners. The safety of the four-drug regimen in pregnancy and lactation is unknown.

The regimens have been studied in untreated or previously treated patients with or without cirrhosis[2-6] (see Table). Patients were treated for 12 or 24 weeks with or without ribavirin. Efficacy was assessed as the proportion of patients who had a sustained virological response. This was defined as having a viral RNA concentration below 25 IU/mL 12 weeks after the end of treatment.

The Sapphire I trial involved 631 patients who were infected with hepatitis C genotype 1, but did not have

Table **Major efficacy trials of a four-drug regimen‡ for hepatitis C genotype 1**

Trial	Patients and treatment	Proportion achieving a sustained virological response§
Untreated patients without cirrhosis		
Sapphire I [2]	473 patients 4-drug regimen and ribavirin	96.2%
Pearl IV [4] (genotype 1a)	205 patients 4-drug regimen	90.2%
	100 patients 4-drug regimen and ribavirin	97%
Pearl III [4] (genotype 1b)	209 patients 4-drug regimen	99%
	210 patients 4-drug regimen and ribavirin	99.5%
Previously treated patients without cirrhosis		
Sapphire II [3]	297 patients 4-drug regimen and ribavirin	96.3%
Pearl II [5] (genotype 1b)	91 patients 4-drug regimen	100%
	88 patients 4-drug regimen and ribavirin	96.6%
Patients with cirrhosis		
Turquoise II [6]	208 patients 4-drug regimen and ribavirin	91.8%
	172 patients 4-drug regimen and ribavirin (24 weeks)	95.9%

‡ The four-drug regimen consisted of paritaprevir, ritonavir and ombitasvir plus dasabuvir given for 12 weeks (unless otherwise stated).
§ A sustained virological response is a concentration of hepatitis C RNA below 25 IU/mL 12 weeks after the end of treatment.

cirrhosis. One group of 473 patients was randomised to take the four-drug regimen with ribavirin for 12 weeks while 158 patients took a placebo regimen. Twelve weeks after their treatment concluded, 96.2% of the patients in the active treatment group had a virological response. Alanine aminotransferase returned to normal in 97% compared with 15% of those given placebo. Patients in the placebo group were later switched to a 12-week course of treatment. Both groups were to be followed up for 48 weeks after treatment to see if the virological response was sustained.[2]

The Sapphire II trial had a similar design but involved 394 patients who had not completely responded, or had relapsed following treatment with peginterferon and ribavirin. The active treatment was again the four-drug regimen plus ribavirin. Twelve weeks after 12 weeks of therapy, 96.3% of the 297 patients who took the active treatment had a sustained virological response.[3]

The Pearl trials compared the efficacy of the four-drug regimen with or without ribavirin in untreated and previously treated patients. All these trials studied 12 weeks of treatment. Twelve weeks after completing this treatment there was a sustained virological response in 90.2% of 205 people infected with genotype 1a who took the four-drug regimen. In the 100 patients who also took ribavirin the response rate was 97%.[4] For the 419 patients infected with genotype 1b the response rate was 99% without ribavirin and 99.5% with ribavirin.[4]

Pearl II was an open-label trial involving 179 patients whose previous treatments for genotype 1b had failed. The sustained virological response was 96.6% with ribavirin and 100% without.[5]

The Turquoise II trial investigated the five-drug regimen in 380 patients with mild (Child-Pugh class A) cirrhosis. Most of these patients had previously been treated with peginterferon and ribavirin. The patients were randomised to receive treatment for 12 or 24 weeks with efficacy assessed 12 weeks after the end of the course. The virological response was 91.8% with a 12-week course and 95.9% with a 24-week course. In previously untreated patients the response rate was 94–95%. Response rates were lower in patients who had not responded to previous therapy or had a history of injecting drugs.[6]

The five-drug regimen has also been tried in patients with hepatitis C genotype 1 and HIV infection. The Turquoise I trial randomised 31 patients to a 12-week course and 32 to a 24-week course. Most (65–69%) of the patients had not been previously treated for hepatitis C. Twelve weeks after treatment concluded the virological response rates were 94% for the 12-week course and 91% for the 24-week course. These regimens did not appear to lead to loss of control of the HIV infection.[7]

A small study has looked at patients who have recurrent infection with genotype 1 hepatitis C after liver transplantation. The 34 patients were treated with the five-drug regimen for 24 weeks. There was a virological response in 97% of the patients 12 weeks after treatment and this was sustained 24 weeks after treatment concluded.[8]

A problem with combination products is that it can be difficult to attribute adverse effects to a particular component. As there is previous experience with ritonavir and ribavirin, some adverse effects can be anticipated, but it may be harder to identify the adverse effects of paritaprevir, ombitasvir and dasabuvir when they are used in combination. While 1.2% of patients had to stop treatment because of adverse events, this was mainly in people treated with ribavirin. Only 0.3% of those taking the four-drug regimen had to discontinue.

The common adverse effects seen in the trials were fatigue, nausea, pruritus and insomnia. These symptoms tended to be more frequent when ribavirin was included in the regimen. Another adverse effect, which is probably due to ribavirin, is anaemia. This may cause problems in patients with cardiovascular disease. Suppression of the hepatitis C virus should see improvements in liver function tests, however, concentrations of alanine aminotransferase increase in some patients.

During the trials the virus developed drug resistance. This led to treatment failure in 3% of patients, usually presenting as a relapse after treatment concluded.

The efficacy of paritaprevir, ritonavir, ombitasvir and dasabuvir makes this combination suitable for treating patients infected with hepatitis C genotype 1b.[4,5] It may be possible to use this combination to treat patients infected with genotype 1a if they have not previously been treated and do not have cirrhosis, but the addition of ribavirin is needed to maximise the response.[4] While the five-drug regimen is very effective, it will require careful selection of patients and checking the product information to avoid drugs that either interact or are contraindicated. As the regimen involves three new drugs, unforeseen problems could emerge in the future. An alternative regimen of ledipasvir and sofosbuvir[9] may be easier to manage and avoids the adverse effects of ribavirin.

T T manufacturer provided additional useful information

REFERENCES *†

1. Thompson AJ, Holmes JA. Treating hepatitis C - what's new? Aust Prescr 2015;38:191-7. http://dx.doi.org/10.18773/austprescr.2015.068
2. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603. http://dx.doi.org/10.1056/NEJMoa1315722
3. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604-14. http://dx.doi.org/10.1056/NEJMoa1401561
4. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al.; PEARL-III Study; PEARL-IV Study. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-92. http://dx.doi.org/10.1056/NEJMoa1402338
5. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359-365.e1. http://dx.doi.org/10.1053/j.gastro.2014.04.045
6. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82. http://dx.doi.org/10.1056/NEJMoa1402869
7. Sulkowski MS, Eron JJ, Wyles D, Trinh R, Lalezari J, Wang C, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA 2015;313:1223-31. http://dx.doi.org/10.1001/jama.2015.1328
8. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med 2014;371:2375-82. http://dx.doi.org/10.1056/NEJMoa1408921
9. Ledipasvir with sofosbuvir for hepatitis C. Aust Prescr 2015;38:217-25. http://dx.doi.org/10.18773/austprescr.2015.078

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

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

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

A:

ANSWERS TO SELF-TEST QUESTIONS

1 True 2 False
3 True 4 False

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

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Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

Fax (02) 6282 6855

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