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CONTENTS

EDITORIAL

Data informs debate E Roughead **38**

ARTICLES

Long-term drug treatment of patients with alcohol dependence P Crowley **41**

How to manage warfarin therapy PA Tideman, R Tirimacco, A St John, GW Roberts **44**

Update on the management of post-traumatic stress disorder D Wallace, J Cooper **55**

Treatment for Alzheimer's disease: has anything changed? LM Waite **60**

DIAGNOSTIC TESTS

Imaging for chronic abdominal pain in adults R Mendelson **49**

LETTERS TO THE EDITOR **39**

FEATURES

Book reviews
The renal drug handbook **48**
Martindale: the complete drug reference **59**

NEW DRUGS **64**

Empagliflozin for type 2 diabetes
Perampanel for epilepsy
Simeprevir for hepatitis C
Umeclidinium bromide/vilanterol for COPD

Data informs debate

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Key words

drug evaluation, drug
information, drug regulation

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When a new medicine enters the market, medical practitioners are faced with questions on whether it is appropriate for their patients, particularly patients with multiple chronic illnesses taking multiple treatments. When the product is first marketed there may be limited information about it. However, regulatory agencies, such as the Therapeutic Goods Administration in Australia, hold a lot of data from clinical trials. If this data were publicly available it could inform clinical practice. Up until now, the publication of information by regulatory agencies has been limited to product assessment reports or summaries.

One of the particular challenges for assessing the place of a new drug in practice is its efficacy or safety compared to other therapies. Despite the fact that we already have drugs for the majority of chronic diseases, we still do not usually test if a new drug is better than current therapy. Of the medicines approved in the European Union in 2009–10, only 28% were tested to determine if they were better.¹

While we are now undertaking more medical research than ever before, gaps in the evidence base are still common. Only 30% of the 84 medicines for chronic conditions approved in Europe between 2000 and 2010 were tested for safety and efficacy in more than 1000 patients for at least 12 months.² In some specialty areas, trials are even smaller and open-label designs are also problematic. Of the oncology trials

registered in the ClinicalTrials.gov database between 2007 and 2010, 72% had 100 participants or less and 88% were open label.³ Limited evidence translates into uncertainty for both regulators and funders when it comes to decisions to register and subsidise new medicines. A European study of 68 applications for marketing in 2009–10 found that for 11 drugs there were major objections about whether a clinically relevant primary endpoint had been used. Despite this, 5 of these 11 were still approved.⁴ Of the 22 medicines where there was doubt or uncertainty about safety issues, 17 were still approved.⁴

Independent re-analysis of the data drug companies submit to regulatory agencies may facilitate a better understanding of the strengths and limitations of the available data for informing clinical practice. The information has often been treated as 'commercial in confidence', but access is improving. In May 2014, European Union Regulation 536/2014 was adopted. This states that 'in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted'. Consequently the European Medicines Agency (EMA) agreed to publish clinical trial reports for products that have been authorised from January 2015.⁵ The trial data will be available for non-commercial purposes for researchers, health professionals and the public, providing an opportunity for reassessment of the data. This is likely to lead to significantly increased debate about the place and safety of new drugs in practice.

There have been a number of examples where access to, and analysis of, regulatory data has created controversy or revised opinion about the place of a therapy in practice. Muraglitazar, the first dual peroxisome proliferator-activated receptor agonist for diabetes, was reviewed for market registration in the USA, and in September 2005 the Endocrinologic and Metabolic Drugs Advisory Committee of the US Food and Drug Administration (FDA) voted in favour of approving the drug. However, a concurrent independent analysis of the publicly available data submitted to the FDA found muraglitazar was associated with an increased risk of adverse cardiovascular outcomes.⁶ Subsequently, market authorisation has not progressed.

Re-analysis of publicly available FDA data also featured in the controversy concerning the cardiovascular safety of rofecoxib.⁷ This contributed to the drug's withdrawal.

From the Editor



Compared to when the ANZACs landed at Gallipoli 100 years ago this month, there is now a greater understanding of post-traumatic stress disorder. Duncan Wallace and John Cooper update us on how to manage this condition.

Patients with post-traumatic stress disorder may also have problems related to alcohol abuse. Philip Crowley explains how drug treatment can help the management of alcohol dependence.

Heavy drinking can interfere with anticoagulant treatment. Philip Tideman, Rosy Tirimacco, Andrew St John and Gregory Roberts include alcohol consumption as one of the factors to consider when optimising warfarin therapy.

Patients drinking heavily may develop abdominal symptoms. Richard Mendelson provides advice on how to use imaging to investigate abdominal pain.

While there have been improvements in imaging techniques, the drug treatment of dementia has not advanced. Louise Waite discusses the direction of research in Alzheimer's disease. When this research is complete, it will be important to have access to the trial data, as Libby Roughead points out that greater scrutiny will help to ensure that new drugs are safe and effective.

Most recently, publicly available data from both the EMA and the FDA has created debate about both the appropriate dose of the oral anticoagulant dabigatran and the need to monitor its concentration.⁸ Review of the FDA's reports revealed that an advisory committee had voted six to four in favour of a 110 mg formulation. However, despite this advice only a 150 mg dabigatran product was approved in the USA. The material also revealed at least one committee member raised concern about whether dabigatran required laboratory monitoring, given that the data showed variability in plasma concentrations. Review of information from the EMA also revealed individual committee members had concerns about the large variability in plasma concentrations. Appraisal of the materials from both regulatory agencies also highlighted their different responses to the same evidence. The Europeans approved the 110 mg dose to reduce the risk of bleeding, while the FDA was concerned about the efficacy of this dose and therefore approved the 150 mg dose.⁸

These examples demonstrate the challenges for regulatory agencies in assessing evidence. However, this challenge is not limited to regulatory

agencies – even re-analysis of trial results by the original study investigators has resulted in changes in interpretation. There has been a study of 37 re-analyses of randomised controlled trials, 86% of which were undertaken by the same research group that published the original trial. Most commonly, the re-analyses used a different method of analysis or used a different definition of the outcome. In 35% of cases, the re-analysis led to different interpretations as to which patients should be treated.⁹

The release of trial data by the EMA in 2015 increases the transparency of the data on which regulatory decisions are made. Future planned developments include the release of individual patient level data, which may further assist in decision making, and potentially enable additional analyses.

Given that there is often uncertainty about either the safety or efficacy of drugs when they first come to market, the provision of trial data in the public domain will spark much more robust debate about the place of medicines in practice. This will allow us to make more informed decisions that meet patients' needs. ◀

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REFERENCES

1. Ujeyl M, Schlegel C, Walter S, Gundert-Remy U. New drugs: evidence relating to their therapeutic value after introduction to the market. *Dtsch Arztebl Int* 2012;109:117-23.
2. Duijnhoven RG, Straus SM, Raine JM, de Boer A, Hoes AW, De Bruin ML. Number of patients studied prior to approval of new medicines: a database analysis. *PLoS Med* 2013;10:e1001407.
3. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA* 2012;307:1838-47.
4. Putzeist M, Mantel-Teeuwisse AK, Aronsson B, Rowland M, Gispén-de Wied CC, Vamvakas S, et al. Factors influencing non-approval of new drugs in Europe. *Nat Rev Drug Discov* 2012;11:903-4.
5. European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. Policy/0070. EMA/240810/2013. London: EMA; 2014.
6. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005;294:2581-6.
7. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;286:954-9.
8. Moore TJ, Cohen MR, Mattison DR. Dabigatran, bleeding, and the regulators. *BMJ* 2014;349:g4517.
9. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, et al. Reanalyses of randomized clinical trial data. *JAMA* 2014;312:1024-32.

Letters to the Editor

Pharmaceuticals, pharmacists and profits

Editor, – In his article, 'Pharmaceuticals, pharmacists and profits: a health policy perspective' (*Aust Prescr* 2014;37:148-9), Professor Philip Clarke highlights the importance of the price disclosure policy in reducing government spending on pharmaceuticals. However, Professor Clarke blatantly disregards the important role that community pharmacists play by comparing pharmacies to 'firms that sell computers or mobile

phones'. He asks why community pharmacy should have the support of taxpayer funds in order to remain viable while electronics stores do not. What a ridiculous comparison!

Community pharmacies are staffed by highly trained health professionals and are essential in providing timely access to prescription medicines. This is an essential service that must remain a viable business for those involved. In addition to this, community pharmacists also provide a range of



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.

important services including counselling on the use of medicines, drug information and advice, primary health care, medication management services and delivery of medicines to the elderly and disabled. These services are generally provided free of charge and help to reduce medication-related hospital admissions which cost \$1.2 billion annually.

Australian pharmacists are well attuned to the need to ensure that the Pharmaceutical Benefits Scheme (PBS) remains sustainable, especially in the context of our ageing population. They are calling for increased opportunities to provide funded health care and medication management services.

Pharmacists remain one of the most accessible health professionals with anyone being able to walk into a pharmacy (often open long hours) and obtain advice within 10 minutes. Community pharmacies are ideally placed to provide an expanded range of services where current gaps exist.

Melanie Frodsham
Pharmacist
Melbourne

Dr Philip Clarke, the author of the article, comments:

 I fully agree with Ms Frodsham that community pharmacies are staffed by highly trained professionals who can play an important role in providing advice and information on the use of medicines to improve health outcomes. However, it is very unclear why this role depends on the pharmacy owners continuing to receive government subsidies from 'discounts' on the wholesale cost of generic drugs. These discounts mean that payments from government to pharmacies exceed the regulated markups of many generic drugs. This costs taxpayers hundreds of millions of dollars each year.

Paying high prices for generic drugs not only has a financial impact on some patients, but it also increases the chance they may discontinue their treatment, which may put them at risk. A far better way to remunerate pharmacists would be to look at ways to directly pay for the services they provide, rather than the current system, where profitability largely depends on the volume and margins on drugs sold.

Smoking and preoperative assessment

Editor, – The article on preoperative assessment (Aust Prescr 2014;37:188-91) was a good review, but unfortunately omitted the critical issue of smoking. Smoking causes increased cardiorespiratory

complications, intensive care admissions, mortality, wound infections and poorer wound healing after surgery. Smoking cessation before elective surgery can significantly improve postoperative outcomes.¹ The perioperative period is a teachable moment when patients are more motivated to quit,² and some patients who quit may remain abstinent after discharge. However, many opportunities to assist smokers are being missed and most continue to smoke up to the day of surgery.³

The Australian and New Zealand College of Anaesthetists recommends a simple and brief intervention known as the A-A-R strategy.⁴ It involves:

- Asking about smoking status
- Advising smokers to quit
- Referring them for smoking cessation support.

Smokers can be referred to Quitline (137 848), general practitioners or Tobacco Treatment Specialists (www.aascp.org.au). A brief smoking intervention such as Ask Advise and Refer should be a routine part of preoperative elective surgery care for all anaesthetists and surgeons.

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Colin Mendelsohn has received honoraria for teaching, consulting and travel from Pfizer, GlaxoSmithKline, and Johnson & Johnson. He sits on Pfizer's Champix Advisory Board.

REFERENCES

1. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. *Am J Med* 2011;124:144-54.
2. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *Anesthesiology* 2010;112:102-7.
3. Webb AR, Robertson N, Sparrow M. Smokers know little of their increased surgical risks and may quit on surgical advice. *ANZ J Surg* 2013;83:753-7.
4. Australian and New Zealand College of Anaesthetists (ANZCA). Guidelines on smoking as related to the perioperative period. Melbourne: ANZCA; 2014.

Austin Ng and Leonard Kritharides, the authors of the article, comment:

 We appreciate the important comments made by Dr Mendelsohn. We certainly agree smoking cessation is important for all patients including those undergoing surgery. It should be incorporated into a protocol-driven documentation of the patient's risk factors during preoperative assessment as recommended by the Australian and New Zealand College of Anaesthetists.

Long-term drug treatment of patients with alcohol dependence

SUMMARY

Drug therapy for alcohol dependence should only be used in conjunction with a comprehensive treatment plan.

Naltrexone and acamprosate have well established efficacy and are first-line treatments.

Naltrexone is recommended for patients aiming to cut down their alcohol intake who do not have severe liver disease or an ongoing need for opioids.

Acamprosate is recommended for those who have achieved and wish to maintain abstinence.

Disulfiram is no longer considered first-line treatment due to difficulties with compliance and toxicity.

Although baclofen and topiramate have evidence of benefit, they are not registered for alcohol dependence and should only be considered in specialist practice.

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Key words

acamprosate, alcohol
dependence, baclofen,
disulfiram, naltrexone,
topiramate

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Introduction

Alcohol dependence is typically a chronic, relapsing condition in which there is evidence of significant change in the motivation and control systems in the brain.¹ Increasingly drug therapy is focused not just on the treatment of the acute withdrawal syndrome, but on modifying these other dysregulated brain systems. It should be used in conjunction with a comprehensive treatment plan that includes appropriate psychological and rehabilitation strategies, with the aim of reducing alcohol craving, compulsive use and impaired control. There is evidence that pharmacotherapy for alcohol dependence is underused.²

Alcohol use disorders can range from mild to severe. Pharmacotherapy is generally used for people with more severe disease. In Australia, there are three drugs currently approved – oral naltrexone, acamprosate and disulfiram. Only naltrexone and acamprosate are subsidised on the Pharmaceutical Benefits Scheme (PBS). Two others, baclofen and topiramate, are now used in specialist practice but are not approved for alcohol dependence.

Naltrexone

Naltrexone is a mu opioid receptor antagonist. It has high receptor affinity that reduces the reinforcing euphoric reward of alcohol. Naltrexone is listed on the PBS as an authority item for alcohol dependent individuals as part of a comprehensive treatment plan with a goal of abstinence. It is also recommended for patients seeking to reduce heavy drinking.³

Naltrexone reduces relapse rates after abstinence⁴ and also helps reduce heavy drinking in people who continue drinking during treatment.⁵ It may be given in combination with acamprosate but there is conflicting evidence for the benefit of this combination over monotherapy. It has a slightly larger effect size than acamprosate, but has more adverse effects including headache, nausea, lethargy and dysphoria. These effects are usually transient and rarely lead to cessation of therapy.

Naltrexone is an opioid antagonist so it should not be used in patients receiving long-term opioid therapy. If opioids are needed in an acute situation, naltrexone should be stopped. Naltrexone is contraindicated in acute hepatitis or liver failure, and liver function should be monitored **monthly** during therapy. Treatment is not advised in people who have alanine aminotransferase concentrations greater than 3–5 times the normal limit.

Naltrexone comes in different forms, but not all are approved in Australia. The usual dose is 50 mg a day orally, starting 4–7 days after the last drink. Naltrexone can also be used in people who are still drinking as it may help them to cut down. Patients are often started on a half tablet (25 mg) daily for the first 3–5 days to minimise adverse effects. There are no specific ill effects from alcohol consumption during treatment and patients do not need to be advised to stop therapy if they relapse.

Acamprosate

Acamprosate is a structural analogue of gamma-aminobutyric acid (GABA). It is thought to work by

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The word 'monthly' was removed.

affecting calcium channels and modifying transmission along GABA and glutamine pathways in the brain.⁶ This may result in decreased positive reinforcement of alcohol intake and withdrawal cravings.

Acamprosate should be considered first-line treatment for patients with alcohol dependence seeking to maintain abstinence. Five meta-analyses concluded that abstinence was significantly higher with acamprosate.⁶ In addition, some evidence suggests that it protects neurons from damage and death caused by the effects of alcohol withdrawal-associated neurotoxicity.⁷

Acamprosate is generally well tolerated. The most common adverse event is transient diarrhoea. It has no abuse potential and does not interact with alcohol or drugs commonly prescribed in people with alcoholism such as antidepressants, anxiolytics, disulfiram, naltrexone and neuroleptics. It can be given to patients with liver dysfunction.

The recommended dose is two 333 mg tablets, three times a day for people over 60 kg. Guidelines recommend acamprosate is started 5–7 days after the patient's last drink, but it can be safely started during withdrawal.³ Its three-times-daily dosing regimen may contribute to its reduced adherence.

Disulfiram

Disulfiram is a deterrent drug that does not directly influence motivation to drink. It inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde. Drinking alcohol within two weeks of taking disulfiram results in the accumulation of acetaldehyde in the blood. This causes unpleasant effects such as sweating, headache, dyspnoea, flushing, sympathetic overactivity, palpitations, nausea and vomiting. Seizures, coma and death can occur. Patients should be educated about avoiding unintended sources of alcohol.

There is a high rate of non-adherence with this drug which can be improved when disulfiram administration is directly observed by a friend, relative or pharmacist. The maintenance dose is 200 mg daily (maximum 300 mg). Due to the risk of significant toxicity and limited evidence of effectiveness some clinical practice guidelines do not recommend disulfiram for routine use.⁸ Informed consent discussion should be documented.

Baclofen

Baclofen is a stereoselective GABA receptor agonist. It has been used since the 1920s to control spasticity.⁹ Much of alcohol's acute effects on the central nervous system are mediated by its stimulation of the GABA system, which is neuroinhibitory.¹⁰

In animals, baclofen reduces alcohol's reinforcing, rewarding, stimulating and motivational properties.^{11,12} It has been shown to reduce the risk of relapse in high-risk drinkers^{13–16} and seems most suited to patients who have more chronic and severe disease and a history of regular high-dose drinking, including those with advanced liver disease.¹⁴ It is primarily aimed at drinkers seeking to maintain abstinence but is not approved for this indication in Australia.

Baclofen is highly toxic in overdose and should be used with caution in patients with a history of overdose or other substance use as well as those with a history of psychotic illness or renal insufficiency.¹⁷ Patients at risk of suicide were often excluded from trials.

The baclofen dose needs careful titration over weeks, beginning with 5 mg three times a day. The optimum dose generally ranges between 30 mg and 75 mg. Adverse effects include sedation and impairment of ability to drive or use machinery. These are exacerbated by concurrent alcohol. Baclofen may also cause nausea, visual disturbance and urinary disturbance. Abrupt cessation may result in seizures or confusion.

Topiramate

Topiramate, a sulfamate-substituted monosaccharide related to fructose, is an antiepileptic with neuroprotective properties. It reduces the rewarding effects of acute alcohol use by suppressing dopamine release, and normalises dopamine activity in chronic alcohol use. This reduces cravings for alcohol and withdrawal symptoms.¹⁸ Topiramate has mood stabilising properties and may be efficacious in bipolar disorder, borderline personality disorder and post-traumatic stress disorder. As alcohol use is often comorbid with psychiatric disorders, topiramate may be viewed as a way to address multiple disorders with one drug.¹⁹

The therapeutic effects of topiramate appear to be robust and there is evidence of better outcomes than with acamprosate, naltrexone or disulfiram.¹⁸ However, it is not approved in Australia for alcohol dependence.

Adverse effects are generally mild to moderate but include dizziness, paraesthesia, psychomotor slowing, memory or concentration impairment and weight loss. A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has occasionally been reported. If there are sudden vision changes, eye pain or redness then topiramate should be ceased and medical review arranged.

Topiramate can be commenced before cessation of alcohol.¹⁸ Dosing requires slow titration from 25 mg daily to a maximum of 150 mg twice daily.

General points for managing alcohol dependence long term

People who have long-term alcohol dependence often have other social, psychological and physical difficulties. These should be addressed with a comprehensive treatment plan.

The usual medication treatment period is at least 3–6 months, but the decision on treatment duration should be made on a case-by-case basis. Long-term follow-up of patients after an intensive treatment program is recommended. Drug treatment needs to be combined with counselling and psychological therapies.³

Naltrexone has been used cautiously in pregnancy due to an absence of known harmful effects, but acamprosate, disulfiram, baclofen and topiramate are contraindicated. Consultation with a specialist is recommended for patients using multiple medicines or with serious medical or psychiatric conditions.

Thiamine

Thiamine administration is important for patients withdrawing from alcohol. Treatment is subsidised on the PBS for Aboriginal and Torres Strait Islander people. There is evidence that parenteral thiamine is underused and that oral therapy is often ineffective.

Australian guidelines recommend that healthy patients with a good diet take oral thiamine 300 mg per day for 3–5 days, then 100 mg for a further 4–9 days. For chronic drinkers who have a poor diet, intramuscular or intravenous thiamine 300 mg per day for 3–5 days is recommended, followed by oral thiamine 300 mg per day for several weeks.³

Conclusion

Alcohol dependence fits a chronic disease model. Primary care uptake of pharmacotherapeutic drugs for long-term alcohol relapse prevention remains insufficient. Naltrexone and acamprosate are first-line treatments with well established efficacy. Naltrexone is recommended for patients aiming to cut down alcohol but cannot be used in those who have severe liver disease or need opioids. Acamprosate is recommended for people who have achieved abstinence and want to maintain it.²⁰ Disulfiram is no longer considered first-line treatment due to difficulties with adherence and toxicity. Baclofen and topiramate have evidence of benefit but are not approved in Australia for this indication and should be used only after specialist consultation. ◀

Conflict of interest: none declared

REFERENCES

1. World Health Organization. International Classification of Diseases (ICD). ICD-10. Geneva: WHO; 2010.
2. Harris AH, Kivlahan DR, Bowe T, Humphreys KN. Pharmacotherapy of alcohol use disorders in the Veterans Health Administration. *Psychiatr Serv* 2010;61:392-8.
3. Australian Government Department of Health and Ageing. Guidelines for the treatment of alcohol problems. Canberra: Commonwealth of Australia; 2009.
4. Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol* 2005;8:267-80.
5. Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, et al. The status of naltrexone in the treatment of alcohol dependence: specific effects on heavy drinking. *J Clin Psychopharmacol* 2006;26:610-25.
6. Mason BJ, Heyser CJ. The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. *Expert Opin Drug Saf* 2010;9:177-88.
7. Mann K, Kiefer F, Spanagel R, Littleton J. Acamprosate: recent findings and future research directions. *Alcohol Clin Exp Res* 2008;32:1105-10.
8. VA/DoD Clinical practice guideline for management of substance use disorders (SUD). Department of Veterans Affairs, Department of Defense. Version 2. Washington, DC: Department of Veterans Affairs; 2009. p. 67.
9. Davidoff RA. Antispasticity drugs: mechanisms of action. *Ann Neurol* 1985;17:107-16.
10. Wang LL, Yang AK, He SM, Liang J, Zhou ZW, Li Y, et al. Identification of molecular targets associated with ethanol toxicity and implications in drug development. *Curr Pharm Des* 2010;16:1313-55.
11. Maccioni P, Carai MA, Kaupmann K, Guery S, Froestl W, Leite-Morris KA, et al. Reduction of alcohol's reinforcing and motivational properties by the positive allosteric modulator of the GABA(B) receptor, BHF177, in alcohol-preferring rats. *Alcohol Clin Exp Res* 2009;33:1749-56.
12. Duke AN, Kaminski BJ, Weerts EM. Baclofen effects on alcohol seeking, self-administration and extinction of seeking responses in a within-session design in baboons. *Addict Biol* 2014;19:16-26.
13. Addolorato G, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Ability of baclofen in reducing alcohol craving and intake: II--Preliminary clinical evidence. *Alcohol Clin Exp Res* 2000;24:67-71.
14. Leggio L, Ferrulli A, Zambon A, Caputo F, Kenna GA, Swift RM, et al. Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. *Addict Behav* 2012;37:561-4.
15. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007;370:1915-22.
16. Flannery BA, Garbutt JC, Cody MW, Renn W, Grace K, Osborne M, et al. Baclofen for alcohol dependence: a preliminary open-label study. *Alcohol Clin Exp Res* 2004;28:1517-23.
17. Dore GM, Lo K, Juckes L, Bezvan S, Latt N. Clinical experience with baclofen in the management of alcohol-dependent patients with psychiatric comorbidity: a selected case series. *Alcohol Alcohol* 2011;46:714-20.
18. Johnson BA, Ait-Daoud N. Topiramate in the new generation of drugs: efficacy in the treatment of alcoholic patients. *Curr Pharm Des* 2010;16:2103-12.
19. Del Re AC, Gordon AJ, Lembke A, Harris AH. Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. *Addict Sci Clin Pract* 2013;8:12.
20. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013;108:275-93.

How to manage warfarin therapy

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anticoagulants, INR, point-
of-care services, warfarin

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This article has a continuing
professional development
activity for pharmacists
available at
[www.australianprescriber.com/
continuing-professional-
development](http://www.australianprescriber.com/continuing-professional-development)

SUMMARY

Long-term treatment with warfarin is recommended for patients with atrial fibrillation at risk of stroke and those with recurrent venous thrombosis or prosthetic heart valves.

Patient education before commencing warfarin – regarding signs and symptoms of bleeding, the impact of diet, potential drug interactions and the actions to take if a dose is missed – is pivotal to successful use.

Scoring systems such as the CHADS₂ score are used to determine if patients with atrial fibrillation are suitable for warfarin treatment. To rapidly achieve stable anticoagulation, use an age-adjusted protocol for starting warfarin.

Regular monitoring of the anticoagulant effect is required. Evidence suggests that patients who self-monitor using point-of-care testing have better outcomes than other patients.

Introduction

Warfarin is recommended for the prevention of systemic embolism, stroke associated with atrial fibrillation, and venous thromboembolism (Table 1).¹ Its use is limited by several factors including a narrow therapeutic range, and drug–drug and drug–food interactions. Bleeding, particularly in the setting of over-anticoagulation, is a major concern.

The decision to start warfarin therapy requires an assessment of its harms and benefits for each patient. This assessment should take into account the patient's medical, social, dietary and drug history, level of education and adherence to previous therapy.² While the risk of falls plays a part in the harm–benefit assessment, published data indicate the propensity to fall is not an important factor in this decision.³

Educating the patient is essential before they start warfarin. This includes informing them about the signs and symptoms of bleeding, the impact of diet, potential drug interactions and actions to take if a dose is missed.

The safety and efficacy of warfarin is critically dependent on maintaining the INR within the target range. Patients must agree to undergo regular blood tests during treatment.

Stroke prevention

In patients with non-valvular atrial fibrillation, the decision to start warfarin should be based on the CHADS₂ score. This assigns 1 point each for congestive heart failure, hypertension, age 75 years and older, and diabetes mellitus, and 2 points for previous ischaemic stroke or transient ischaemic attack.¹

The CHADS₂ score reliably identifies patients at intermediate and high risk of stroke, but less reliably identifies those truly at low risk.⁴ Anticoagulation with

warfarin is recommended if the CHADS₂ score is ≥ 2 and should be considered if the score is 1.

The CHA₂DS₂-VASc score (Table 2),⁵ introduced by the European Society of Cardiology, provides a more comprehensive assessment of the risk factors for stroke. It is better at identifying 'truly low-risk' patients with atrial fibrillation, and is now preferred over CHADS₂. The HAS-BLED score (Table 2)⁵ has been developed to determine the risk of bleeding. Scores range from 0 to 9. Scores ≥ 3 indicate a high risk of bleeding, the need for cautious management and regular review of the patient. It is not the intention to use HAS-BLED scores to exclude warfarin, but to allow the clinician to identify risk factors for bleeding and to correct those that are modifiable.⁶

Optimising warfarin management

A patient's response to warfarin is driven primarily through genetic variance in the hepatic clearance, and vitamin K handling. Diet, age and dose also influence the anticoagulant effect. Assessing the response is complicated by a delay of 2–3 days before the INR reflects any changes in warfarin dose.

Starting warfarin

When commencing warfarin it is important to measure the baseline INR. If this is 1.4 or above, without warfarin, liver function and nutrition status should be assessed and specialist advice sought regarding the patient's suitability for anticoagulation with warfarin.

Warfarin is usually started with loading doses. The Fennerty warfarin loading protocol published in 1984 was efficient in the relatively young population tested, but it was subsequently shown to cause significant over-anticoagulation in the elderly.^{7,8} Another protocol,

Table 1 Indications, goals and duration of warfarin therapy¹

Indication	Target INR (range)	Duration of therapy
Deep vein thrombosis of the leg or pulmonary embolism	2.5 (2.0–3.0)	At least 3 months
Atrial fibrillation or flutter		
Intermediate to high risk of stroke	2.5 (2.0–3.0)	Indefinite
Elective cardioversion	2.5 (2.0–3.0)	3 weeks before scheduled cardioversion and for 4 weeks after successful cardioconversion
Mitral stenosis	2.5 (2.0–3.0)	Indefinite
After stent placement and high risk of stroke	2.5 (2.0–3.0)	Bare-metal stent (1 month) and drug-eluting stent (3–6 months) as triple therapy with clopidogrel and aspirin After initial triple therapy, continue warfarin and a single antiplatelet drug until 12 months after stent placement After 12 months, use warfarin alone
Valvular heart disease		
Rheumatic mitral valve disease	2.5 (2.0–3.0)	Long term
Mechanical prosthetic heart valves	Bileaflet or tilting-disk valves: 2.5 (2.0–3.0) in the aortic position and 3.0 (2.5–3.5) in the mitral position	Long term Recommended to use aspirin in addition, 50–100 mg daily, if low bleeding risk
Bioprosthetic valves in the mitral position	2.5 (2.0–3.0)	3 months after insertion

Table 2 Scoring systems for assessing the risk of stroke (CHA₂DS₂-VASc) and bleeding (HAS-BLED) in patients with atrial fibrillation⁵

CHA ₂ DS ₂ -VASc	Score	HAS-BLED	Score
Congestive heart failure	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function (1 point each)	1 or 2
Age ≥75 years old	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/predisposition	1
Stroke/transient ischaemic attack/thromboembolism	2	Labile INRs (if on warfarin)	1
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1	Elderly (e.g. age >65 years old)	1
Age 65–74 years old	1	Drugs or alcohol (1 point each)	1 or 2
Sex category (i.e. female sex)	1		
Maximum score	9	Maximum score	9

based on the Fennerty protocol, decreased the loading dose with increasing age. This age-adjusted protocol (Table 3*)⁹ recommends a 10 mg starting

dose for patients aged 50 years and under, decreasing to 6 mg for patients over 80 years old.

The age-adjusted protocol was superior to the Fennerty protocol and to empirical prescribing.⁸

Patients more rapidly achieved a stable INR, had fewer results above 4.0 during the initiation phase and fewer doses withheld due to rapidly rising INRs.^{8,9}

* Table 3: Age-adjusted protocol for starting warfarin. See online with this article at www.australianprescriber.com/magazine/38/2/44/8

Warfarin can be safely started in the community setting, but a recognised initiation protocol should be used. Even purportedly 'safe' starting doses of 5 mg represent a large loading dose for a patient who requires a maintenance dose of only 1–2 mg, and can lead to marked over-anticoagulation in a few days if INRs are not monitored. There is generally a significant movement in INR on the third or fourth day after starting warfarin, regardless of whether an initiation protocol is adhered to, or a 'safe' dose of 5 mg is used.

When possible, a single strength warfarin tablet should preferably be prescribed so that doses are multiples of one tablet.¹⁰ Patients should take their warfarin once a day at the same time in the evening, with INR testing in the morning. The INR should be measured daily for the first five days.

Maintenance therapy

Once the patient has had two consecutive INRs in the target range, the INR can be measured at increasing intervals depending on its stability. Once the dose and INR are stable, patients can usually be well controlled with 4–6-weekly testing, but some patients will require more frequent testing. Dose adjustment is not required for minor INR fluctuations, if the result remains within the patient's target range.

When adjusting maintenance doses for high or low INR values, it is important to think in terms of adjusting the dose as a percentage-based change. There is a reasonable linear relationship between dose and INR response during maintenance dosing, so a 10% dose increase will result in an increase of approximately 10% in the INR.¹¹ A 1 mg increment is a major adjustment for a patient normally receiving 2 mg daily (50% adjustment), and would result in a major INR change, but not for a patient receiving 10 mg daily (10% adjustment). Table 4 gives an example of the dose changes that may be needed to maintain the INR within a target range of 2–3.

For INR ≥ 5 follow the Australian consensus guidelines.¹² In all cases of out-of-range INRs, possible causes for altered INR should be considered to

determine if they are reversible. For example, if the INR has been elevated by antibiotics it can be expected to fall when the course is finished. This can be factored into the dosing and monitoring requirements.

Warfarin is subject to multiple interactions including:

- diet – for example beetroot, liver, green leafy vegetables (decreased INR)
- drugs that may increase INR – macrolide antibiotics, imidazole antifungals, sulfamethoxazole/trimethoprim, amiodarone, statins, some non-steroidal anti-inflammatory drugs
- weight loss or weight gain
- excess alcohol.

The risk of bleeding is minimised by regularly monitoring the INR, and ensuring the patient understands the action of warfarin and how to recognise the signs of bleeding. Patients should have their INR checked after any dose changes, the addition of any potentially interacting drugs, or dietary changes.

To prevent INRs outside of target range:

- consider potential warfarin–drug interactions
- wait at least 48 hours before testing INR after any change of dose, as earlier testing will not reflect the full response to the dose adjustment
- if INR drifts below the target, avoid excessive increases in dose
- provide ongoing patient education.

Although bleeding can occur in the target range, the risk increases with a rising INR. Elevated INRs between 4.5 and 10, and not associated with bleeding or a high risk of bleeding, can be safely managed by withholding warfarin and carefully monitoring the INR. Vitamin K₁ can be given orally or intravenously to reverse the effect of warfarin in patients with INRs above 10 or those with bleeding or a high risk of bleeding. In patients who are not actively bleeding, it is important to avoid overtreatment as this will make it difficult to re-establish control of the INR. The initial intravenous dose of vitamin K should

Table 4 Suggested dose changes for maintaining INR within a target range of 2–3

INR	Dose change
<1.5	Increase by 20%
1.6–1.9	Increase by 10%
3.1–3.4	Decrease by 10%, adjustment may not be necessary
3.5–3.9	Decrease by 20%, consider holding one dose
4.0–4.9	Hold dose until INR returns to range then decrease by 20–30%

probably not exceed 0.5–1 mg. If immediate reversal is required, prothrombin complex is preferred to fresh frozen plasma.¹²

Warfarin management strategies

Approaches for managing patients taking warfarin include:

- usual care by the GP
- patient self-monitoring
- laboratory care program.

Anticoagulation clinics coordinate and optimise the delivery of anticoagulant therapy by providing specialised monitoring and management. Patients treated in anticoagulation clinics spend more time in the therapeutic range (50.4% vs 35%). They also experience less significant bleeding (8.1% vs 35%), major or fatal bleeding (1.6% vs 3.9%) or thromboembolic events (3.3% vs 11.8%).¹³ In general practice it should be possible to have patients within the therapeutic range 60% of the time.

Some centres use computer-assisted warfarin dosing.¹⁴ This assists in achieving a stable state of anticoagulation faster, and increases the overall percentage of time in the target range, potentially reducing the frequency of testing. It also reduces the risk of bleeding and thromboembolic events and is more cost-effective than manual dosing using clinical assessment.¹⁵

Point-of-care testing

Point-of-care testing of the INR can be done in general practice, in other locations such as pharmacies, or by the patients themselves (known as self-monitoring). These approaches are more convenient for patients than visits to an anticoagulation clinic in a pathology practice or in a hospital.

The convenience of self-monitoring can be extended further to a model of self-management. Patients use algorithms to determine any necessary dose adjustments following INR measurement.¹⁶ Evidence supports the practice of self-monitoring, with or without self-management, but an essential prerequisite is the ability of the patient to correctly, competently and safely use the testing devices.¹⁷

A number of randomised controlled trials of both self-monitoring and self-management have been included in systematic reviews and meta-analyses.^{16,18–20} In three systematic reviews, self-monitoring and self-management had similar results to routine care in a hospital clinic. Patients undertaking self-monitoring had significant reductions in thromboembolic events and death, with more time in the target range, compared to those who did not self-monitor.^{18–20} A further systematic review of 22 randomised controlled trials showed similar results including a 26% reduction in death.²¹ A recent meta-analysis also found that patients who self-monitored had a reduced risk of thromboembolic events.¹⁶

Few studies have compared INR point-of-care testing by GPs with laboratory testing. A systematic review included three studies, but none showed improvements in the proportion of patients within the target range.²²

An Australian trial of point-of-care testing in general practice included INR testing as well as other tests. While it showed improvements in glycated haemoglobin (HbA1c) and some lipid profiles, there was no such improvement for anticoagulated patients.²³

There is evidence of a poor understanding of INR testing, including therapeutic guidelines, among physicians and GPs in several countries, including Australia.²⁴ The possibility remains that the improved outcomes achieved by self-management may be because patients more consistently follow therapeutic guidelines, especially if they manage their doses using software algorithms.

Conclusion

Warfarin can be a challenging drug to manage, but if used appropriately it can be effective for the prevention of systemic embolism, stroke associated with atrial fibrillation, and venous thromboembolism. Regular monitoring and good patient education are important for successful treatment. ◀

Conflict of interest: none declared

REFERENCES

1. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(Suppl 2):7S–47S.
2. Jaffer A, Bragg L. Practical tips for warfarin dosing and monitoring. *Cleve Clin J Med* 2003;70:361–71.
3. Man-Song-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159:677–85.
4. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: a nationwide cohort study. *Thromb Haemost* 2012;107:1172–9.
5. Lane DA, Lip GY. Use of the CHA2DS2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation* 2012;126:860–5.
6. Amerena JV, Walters TE, Mirzaee S, Kalman JM. Update on the management of atrial fibrillation. *Med J Aust* 2013;199:592–7.

ARTICLE

Warfarin therapy

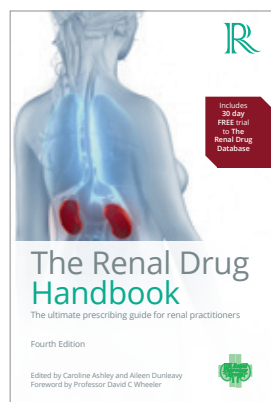
7. Fennerty A, Dolben J, Thomas P, Backhouse G, Bentley DP, Campbell IA, et al. Flexible induction dose regimen for warfarin and prediction of maintenance dose. *Br Med J (Clin Res Ed)* 1984;288:1268-70.
8. Roberts GW, Druskei T, Jorgensen LE, Wing LM, Gallus AS, Miller C, et al. Comparison of an age adjusted warfarin loading protocol with empirical dosing and Fennerty's protocol. *Aust N Z J Med* 1999;29:731-6.
9. Roberts GW, Helboe T, Nielsen CB, Gallus AS, Jensen I, Cosh DG, et al. Assessment of an age-adjusted warfarin initiation protocol. *Ann Pharmacother* 2003;37:799-803.
10. Guidelines and Protocols Advisory Committee. Warfarin therapy management. British Columbia, Canada: British Columbia Ministry of Health; 2010. www.bcguidelines.ca/guideline_warfarin_management.html [cited 2015 Mar 3]
11. Holford NH. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin Pharmacokinet* 1986;11:483-504.
12. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS, et al. An update of consensus guidelines for warfarin reversal. *Med J Aust* 2013;198:198-9.
13. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. *Arch Intern Med* 1998;158:1641-7.
14. Wright DF, Duffull SB. A Bayesian dose-individualization method for warfarin. *Clin Pharmacokinet* 2013;52:59-68.
15. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. *Br J Haematol* 2011;154:311-24.
16. Heneghan C, Ward A, Perera R; Self-Monitoring Trialist Collaboration, Bankhead C, Fuller A, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;379:322-34.
17. Self-monitoring for patients on warfarin? *Evid Based Med* 2010;15:161-4.
18. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet* 2006;367:404-11.
19. Christensen TD, Johnsen SP, Hjortdal VE, Hasenkam JM. Self-management of oral anticoagulant therapy: a systematic review and meta-analysis. *Int J Cardiol* 2007;118:54-61.
20. Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, et al. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev* 2010;4. CD003839.
21. Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med* 2011;154:472-82.
22. Gialamas A, St John A, Laurence CO, Bubner TK; PoCT Management Committee. Point-of-care testing for patients with diabetes, hyperlipidaemia or coagulation disorders in the general practice setting: a systematic review. *Fam Pract* 2010;27:17-24.
23. Bubner TK, Laurence CO, Gialamas A, Yelland LN, Ryan P, Willson KJ, et al. Effectiveness of point-of-care testing for therapeutic control of chronic conditions: results from the PoCT in General Practice Trial. *Med J Aust* 2009;190:624-6.
24. Kristoffersen AH, Thue G, Ajzner E, Claes N, Horvath AR, Leonetti R, et al. Interpretation and management of INR results: a case history based survey in 13 countries. *Thromb Res* 2012;130:309-15.

Book review

The Renal Drug Handbook. 4th ed.

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Ashley C, Dunleavy A

London: Radcliffe Publishing; 2014.

1016 pages

Also available in online database format

www.renaldrugdatabase.com

This handbook provides detailed drug information to assist healthcare professionals to safely dose medications in patients with kidney disease. It is also available online which I suspect will extend the readership from predominantly renal pharmacists to other groups.

The Preface outlines how to use the monographs and basic drug dosing advice including valuable information on the use of estimated glomerular filtration rate (eGFR).

Over 800 drug monographs are arranged in alphabetical order, making navigation easy. Each monograph has a standard format, which includes information about the drug's clinical use, its dose in normal renal function, and its pharmacokinetics and metabolism. If a dose reduction is required in renal impairment, the dose is given either in milligrams with

the appropriate frequency, or as a percentage of the normal dose. Dosing for patients undergoing renal replacement therapies is also included. If relevant, other useful information about drug interactions, administration, adverse effects more commonly seen in patients with kidney impairment and monitoring is also included.

The section on pharmacokinetics is particularly useful as it gives the prescriber access to information so that first principles can be applied. Although I would like to have seen more referencing within the individual monographs, a list of texts and websites is included in the Preface.

One limitation is that the handbook is a UK publication so some of the drugs and dosing recommendations are not relevant to the Australian situation. Perhaps a consideration for future editions might be to include some general comments on the use of various drug classes in patients with renal disease.

Overall I applaud the authors for updating this publication, which is an extremely useful resource for guiding prescribing in patients with kidney impairment.

Imaging for chronic abdominal pain in adults

SUMMARY

Diagnostic imaging is often not indicated in chronic abdominal pain. In particular, undifferentiated abdominal pain is rarely an indication for a CT scan.

CT scanning is overused even when imaging is required. Other modalities may be preferable. A normal CT scan does not rule out cancer.

Alarm symptoms, including anaemia, blood in the stool, waking at night with gastrointestinal symptoms, and weight loss, should be investigated. The most appropriate modality depends on the symptoms.

Clinical information on request forms for CT scans should be specific and include the suspected condition as this helps the radiologist to determine an appropriate imaging protocol.

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Key words

abdominal pain, Crohn's
disease, gallstones, imaging,
irritable bowel syndrome

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Introduction

Chronic abdominal pain is common in primary care. It is defined as continuous or intermittent abdominal discomfort lasting for at least six months. It may arise from the gastrointestinal tract or adjoining organs, such as the biliary tract or pancreas, or have a gynaecological or genitourinary origin. In many cases, chronic abdominal pain is part of a functional syndrome.

CT of the abdomen is a frequently requested and performed examination for abdominal pain. In 2012-13 there were over 330 000 such Medicare services at a cost of \$146 million. Many of the scans were for non-specific abdominal pain. No data are available for the outcome of these examinations, but in view of the costs as well as the radiation burden to the individual and the community, it is important to ensure that CT of the abdomen is used appropriately. In addition, about 5% of abdominal CT scans will detect 'incidentalomas' unrelated to the patient's symptoms, but often leading to a cascade of further tests resulting in further risk, anxiety and cost.

Diagnostic imaging is often not needed in patients with chronic abdominal pain. When imaging is indicated, a CT scan may not be the ideal investigation. Ultrasound, CT and MRI all have their advantages and disadvantages. Each have their roles, which are not often interchangeable. The risks of ionising radiation with CT should always be considered, particularly in young patients. A non-ionising alternative such as ultrasound or MRI should be chosen if practicable and if it is likely to yield as much diagnostic information. However, if justified (that is, the potential benefit

outweighs the risk), CT should be performed and the patient reassured about the risks.

Ultrasound has the major advantages of safety (no ionising radiation), cost and availability and it can be repeated as often as necessary. However, it is regarded as more operator-dependent than the other modalities. MRI also uses no ionising radiation, although it has several contraindications (including metallic medical devices such as pacemakers, claustrophobia). It is also relatively expensive and access is limited, especially to GPs.

Assessing the patient

In general, clinical localisation of disease by the site of the patient's symptoms is unreliable. However, there is reasonable correlation between epigastric pain and gastroduodenal disease, right upper quadrant pain and hepatobiliary disease, and suprapubic pain and gynaecological causes.¹ It is therefore useful to categorise patients by their predominant presenting features, although there may sometimes be overlap. Categories of presenting features include:

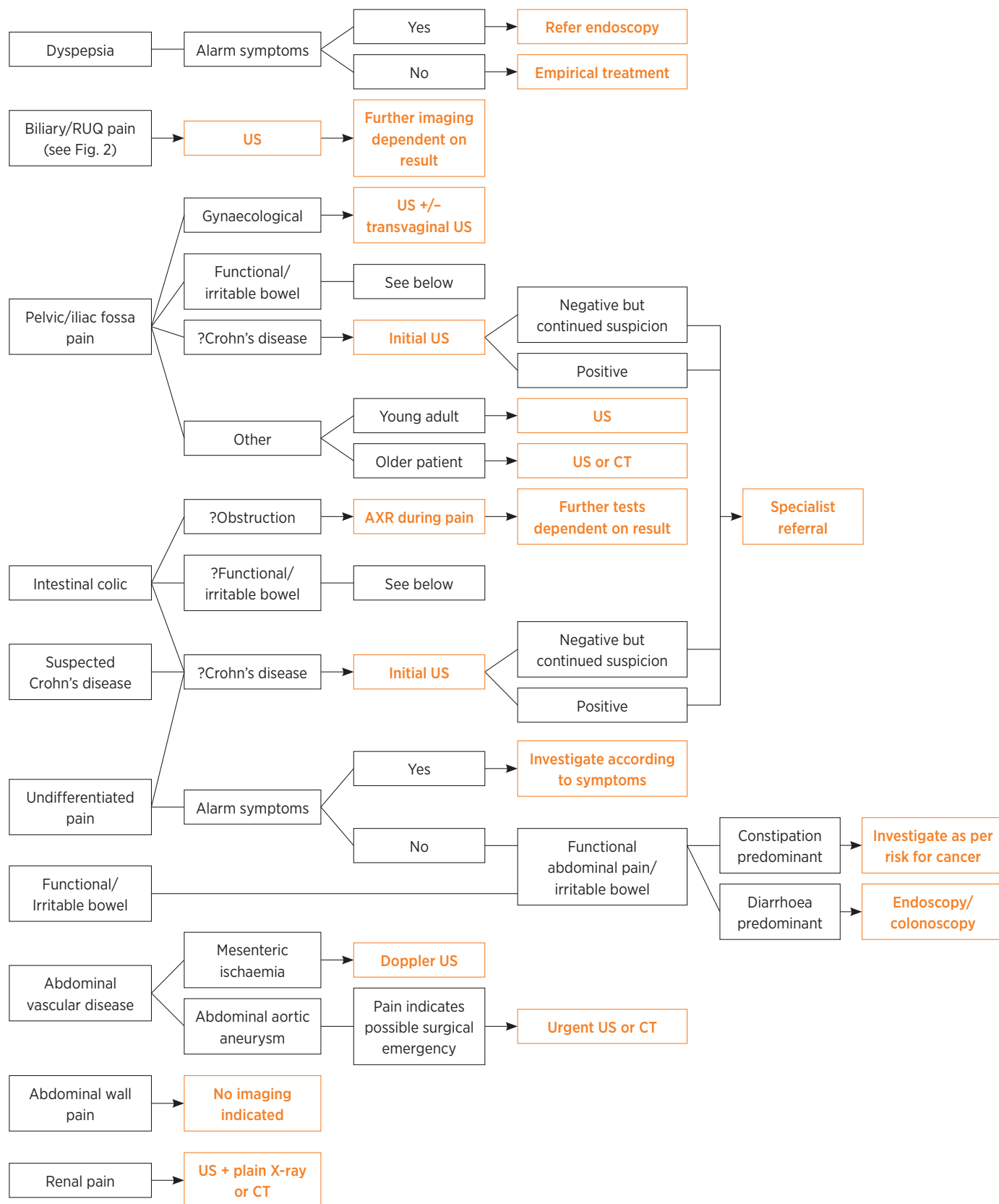
- undifferentiated abdominal pain
- intestinal colic
- symptoms suggesting Crohn's disease
- pelvic or iliac fossa pain, causes of which include gynaecological disease, Crohn's disease and functional syndromes
- dyspepsia
- biliary symptoms or right upper quadrant pain
- renal tract symptoms.

Each of these requires a different approach to diagnostic imaging (see Fig. 1).

DIAGNOSTIC TESTS

Imaging for chronic abdominal pain

Fig. 1 Imaging for chronic abdominal pain in adults



RUQ right upper quadrant US ultrasound AXR abdominal X-ray

Based on 'Diagnostic imaging pathways – abdominal pain (chronic)' at www.imagingpathways.health.wa.gov.au

Undifferentiated chronic abdominal pain

The major causes of undifferentiated abdominal pain are the functional gastrointestinal disorders.² However, inflammatory bowel disease, coeliac disease and mechanical obstruction may need to be excluded. Functional gastrointestinal disorders that may present with pain include irritable bowel syndrome and functional abdominal pain syndrome.

Irritable bowel syndrome

Irritable bowel syndrome is common, affecting about 7% of adults. Although often thought of as a diagnosis of exclusion, a positive diagnosis can be made using symptom complex criteria such as the Rome criteria.^{3,4}

A systematic review of imaging in irritable bowel syndrome concluded that although radiological imaging is frequently used to evaluate patients, there is a striking lack of strong evidence to support this.⁵ Based on the current evidence, further investigations including radiological imaging should only be done in patients who have alarm symptoms, to rule out other structural abnormalities that may mimic irritable bowel syndrome. Early referral to a specialist may be more beneficial than embarking on imaging.

For patients with constipation-predominant irritable bowel syndrome, the need for further investigations should be based on their risk of having colorectal cancer. Those with an above average risk should undergo colonoscopy (or CT colonography, also known as 'virtual colonoscopy'). A CT scan is performed after bowel preparation and insufflation of the colon. CT colonography is widely regarded as superior to barium enema and should replace it.

Most gastroenterologists would recommend colonoscopy in patients with diarrhoea-predominant irritable bowel syndrome to exclude microscopic colitis.

Alarm symptoms

Alarm symptoms that should prompt investigation are:^{5,6}

- A. iron deficiency anaemia
- B. blood in stool
- C. awakening at night with gastrointestinal symptoms
- D. unexplained weight loss
- E. family history of colorectal cancer
- F. age at onset over 50 years.

A, B, C and E should initially be investigated by endoscopy. However, further diagnostic imaging may be required. Pain extending through to the back may be added to the list of alarm symptoms as it can indicate pancreatic disease and should be investigated by CT scanning.

Unexplained weight loss with abdominal pain may require extensive investigation by endoscopy and diagnostic imaging. CT scans can detect a pancreatic lesion or a large gastrointestinal mass, but a normal 'standard' protocol CT scan (that is, without specific bowel preparation) has limited sensitivity for pathology of the bowel.

Functional abdominal pain syndrome

Unlike irritable bowel syndrome, there is no clear relationship to eating or defecation with functional abdominal pain syndrome.⁷ The pain tends to be constant or frequent and is often associated with other somatic symptoms. Imaging is usually not required in the absence of alarm features if all other diagnostic criteria for functional abdominal pain syndrome are present.

Intestinal colic

Colic may be part of a functional syndrome but mechanical obstruction due to inflammatory or neoplastic disease may require exclusion. In patients with suspected mechanical recurrent obstruction, clinical evidence and an X-ray (obtained during an episode of pain) may distinguish small and large bowel disease and indicate the appropriate investigation. Postoperative adhesions are overall the most common cause of recurrent small bowel obstruction. However, further imaging may be required to exclude other causes such as neoplastic or inflammatory disease (e.g. Crohn's disease), especially if there is no past surgical history. This may take the form of CT enterography* or enteroclysis†, or magnetic resonance enterography or enteroclysis.

Large bowel recurrent or subacute obstructive symptoms require urgent investigation. The type of imaging partially depends on whether the patient will tolerate bowel preparation. Specialist referral is warranted.

Suspected Crohn's disease

Ultrasound is a reasonable initial test for suspected Crohn's disease.^{8,9} What follows depends on the level of clinical probability. If this is low, no further imaging may be required since the negative predictive value of ultrasound in this scenario is high. However, if the ultrasound is positive, with non-specific demonstration of thickened loops of bowel, or negative but with continuing clinical suspicion, specialist referral for ileo-colonoscopy is preferable

* enterography involves the ingestion of a large volume of oral contrast before the scan

† enteroclysis is performed by giving contrast medium through a nasojejunal tube

to CT or MRI, which may miss early or localised mucosal disease.

Following a positive diagnosis of Crohn's disease or a negative colonoscopy, but with continued clinical suspicion, CT enterography or enteroclysis, or magnetic resonance enterography or enteroclysis are indicated. When Crohn's disease has been previously confirmed, these scans are to assess the extent and location of disease and the presence of complications.

Pelvic or iliac fossa pain

Causes of pelvic or iliac fossa pain include Crohn's disease, colonic diverticular disease, functional disease and gynaecological disease. In women of reproductive age, when endometriosis or ovarian or other adnexal disease is suspected, pelvic ultrasound (including transvaginal ultrasound when appropriate) is the investigation of choice. In those who do not meet the criteria for irritable bowel syndrome or have red flags, the choice of imaging depends on the provisional clinical diagnosis. Diverticular disease is best initially investigated by CT to look for complications such as pericolic inflammation or chronic abscess. Bear in mind that uncomplicated diverticular disease is extremely common and is very often asymptomatic, and small or even moderate sized cancers cannot be excluded on CT (unless combined with CT colonography, which has a very high negative predictive value).

Dyspepsia

Dyspepsia is defined as a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract. It may include heartburn, acid regurgitation, excessive burping or belching, increased abdominal bloating, nausea, a feeling of abnormal or slow digestion, or early satiety.

Diagnostic imaging has little place in the modern investigation of dyspepsia other than to exclude (by ultrasound) biliary disease as an alternative or concomitant diagnosis, or pancreatic disease if there is clinical suspicion (pain extending through to the back, weight loss, jaundice or abnormal liver function or recent onset of diabetes). CT is indicated for suspected pancreatic disease.

In the absence of red flags, management of dyspepsia is usually with empirical treatment. If red flags are present, or if the patient fails to respond to empirical treatment, investigation is usually by endoscopy.

Red flags indicating early evaluation include:

- age over 55 years and recent onset of symptoms
- daily constant pain
- weight loss
- non-steroidal anti-inflammatory drug use

- vomiting
- a past history of gastric ulcer or gastric surgery
- anaemia
- dysphagia
- gastrointestinal bleeding.

Functional dyspepsia is essentially a diagnosis of exclusion of organic disease.²

Right upper quadrant pain or biliary-type pain

Ultrasound is the first choice of investigation for biliary symptoms or right upper quadrant pain (Fig. 2). It is very accurate at diagnosing or excluding gallstones so if the ultrasound is negative, alternative diagnoses should be considered. If the bile ducts are dilated on an ultrasound scan in the presence of pain, and especially if there are abnormal liver function tests (with or without gallbladder calculi) indicating biliary obstruction, cholangiography and specialist referral are suggested. Biliary obstruction will potentially require surgical or endoscopic intervention.

Cholangiography, initially performed non-invasively with CT cholangiography (if the serum bilirubin is less than twice the upper limit of normal), or magnetic resonance cholangio-pancreatography (MRCP) (independent of the serum bilirubin) are both very accurate at determining the cause of biliary obstruction. In young patients MRCP is preferred because it does not involve ionising radiation.

If the initial ultrasound shows alternative pathology to account for symptoms, such as a peri-ampullary or pancreatic mass, a CT scan and specialist referral are indicated. Functional causes of biliary-type pain also occur,² but organic lesions need to be excluded.

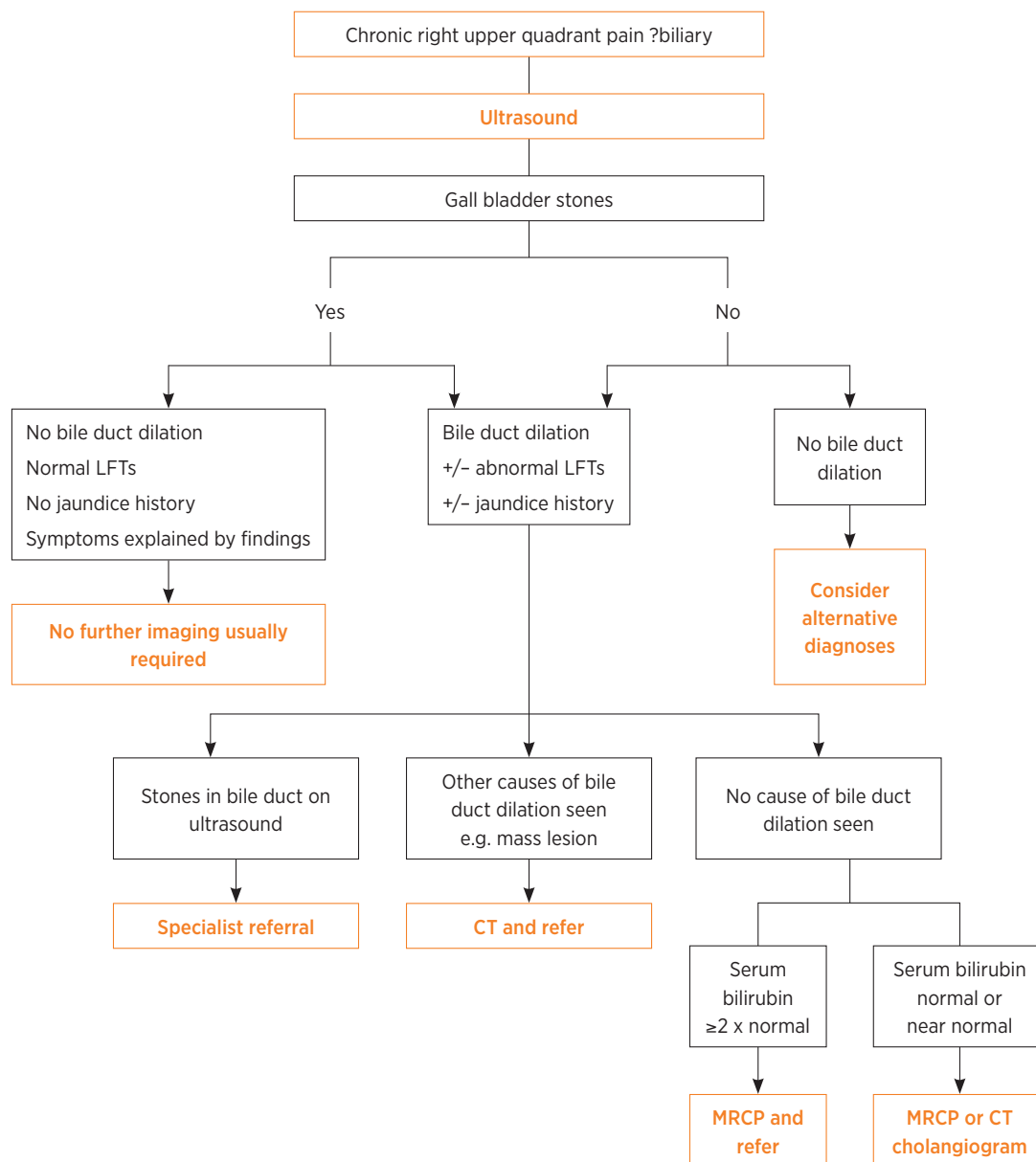
Renal tract symptoms

Pain from the renal tract may be experienced as loin or flank pain. A non-enhanced low-ionising radiation dose CT is indicated if there is an acute exacerbation of pain to exclude ureteric calculi. In younger patients, the combination of a plain X-ray (kidneys-ureters-bladder, KUB) and ultrasound will rule out renal obstruction, intra-renal calculi and renal masses. If the pain is referred to the scrotum, a negative ultrasound of the scrotum should lead to an ultrasound of the whole renal tract. If a renal mass is found, this should be investigated with a multiphase CT scan (CT-IVU, effectively the modern CT equivalent of the conventional intravenous urogram, which is now rarely indicated).

Other conditions

Chronic pain may be caused by vascular conditions such as mesenteric artery stenosis (so-called

Fig. 2 Chronic right upper quadrant pain



LFT liver function test

MRCP magnetic resonance cholangio-pancreatography

Based on 'Diagnostic imaging pathways – upper quadrant pain (chronic right)' at www.imagingpathways.health.wa.gov.au

'mesenteric angina'). This is initially best investigated with Doppler ultrasound. Abdominal aortic aneurysms rarely cause pain until they are large (and usually palpable), and pain is a signal for urgent referral as it may be a sign of imminent leakage.

Chronic abdominal wall pain is an under-recognised condition most commonly due to anterior cutaneous nerve entrapment syndrome. It is characterised by pain that is localised to a highly specific area of the abdomen and is diagnosable by Carnett's test[†].¹⁰

No imaging is indicated for chronic abdominal wall pain and patients usually respond to conservative

[†] Carnett's test involves tensing the muscles of the abdominal wall. The test is positive when the patient's pain is unchanged or worsens, and is indicative of somatic pain arising in the abdominal wall. A negative test (the pain being decreased) is more likely when the pain arises within the abdomen (visceral pain).

DIAGNOSTIC TESTS

Imaging for chronic abdominal pain

management and injection of a local anaesthetic. Similarly, neuropathic pain, for example post-herpetic pain, does not require imaging.

Request forms for imaging

Clinical information on request forms for CT scans should be specific. 'Abdominal pain ?cause' is unhelpful. Even if a CT scan is indicated, the radiologist will be unable to determine the required scanning protocol.

For example, although a request for suspected renal colic and a request for suspected mesenteric angina indicate an abdominal CT scan, the imaging protocol is quite different. The former requires a low-radiation dose non-intravenous contrast (unenhanced) CT, whereas the latter will often require a multiphase scan (pre-contrast, arterial and portal venous phase post-contrast).

'Rule out cancer' is also not helpful on a request form. A normal CT scan does not rule out cancer and may

well give a false sense of security to the patient and their doctor.

Conclusion

Diagnostic imaging in adults with chronic abdominal pain is overused. Even when imaging is indicated, CT scanning is often not the investigation of choice. All imaging investigations should be justified – a responsibility shared by the referrer and the imaging specialist. Providing adequate clinical information to the radiologist is essential to enable the correct modality and the correct protocol to be performed, and to enable proper interpretation of the significance of the test results. ◀

Richard Mendelson is the Editor-in-Chief of 'Diagnostic Imaging Pathways', the clinical decision support tool and educational resource for diagnostic imaging supported by the Government of Western Australia.

REFERENCES

1. Yamamoto W, Kono H, Maekawa M, Fukui T. The relationship between abdominal pain regions and specific diseases: an epidemiologic approach to clinical practice. *J Epidemiol* 1997;7:27-32.
2. Rome Foundation. Guidelines--Rome III diagnostic criteria for functional gastrointestinal disorders. *J Gastrointest Liver Dis* 2006;15:307-12.
3. American College of Gastroenterology task force on irritable bowel syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104 Suppl 1:S1-35.
4. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointest Liver Dis* 2006;15:237-41.
5. O'Connor OJ, McSweeney SE, McWilliams S, O'Neill S, Shanahan F, Quigley EM, et al. Role of radiologic imaging in irritable bowel syndrome: evidence-based review. *Radiology* 2012;262:485-94.
6. Whitehead WE, Palsson OS, Feld AD, Levy RL, VON Korff M, Turner MJ, et al. Utility of red flag symptom exclusions in the diagnosis of irritable bowel syndrome. *Aliment Pharmacol Ther* 2006;24:137-46.
7. Clouse RE, Mayer EA, Aziz Q, Drossman DA, Dumitrascu DL, Mönnikes H, et al. Functional abdominal pain syndrome. *Gastroenterology* 2006;130:1492-7.
8. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology* 2008;247:64-79.
9. Dong J, Wang H, Zhao J, Zhu W, Zhang L, Gong J, et al. Ultrasound as a diagnostic tool in detecting active Crohn's disease: a meta-analysis of prospective studies. *Eur Radiol* 2014;24:26-33.
10. Costanza CD, Longstreth GF, Liu AL. Chronic abdominal wall pain: clinical features, health care costs, and long-term outcome. *Clin Gastroenterol Hepatol* 2004;2:395-9.

FURTHER READING

Government of Western Australia Department of Health. Diagnostic imaging pathways. A clinical decision support tool and educational resource for diagnostic imaging. 2014. www.imagingpathways.health.wa.gov.au [cited 2015 Mar 3]

Quality use of abdominal imaging. In: Health News and Evidence. NPS MedicineWise. 2014. www.nps.org.au/publications/health-professional/health-news-evidence/2014/abdominal-imaging [cited 2015 Mar 3]

Update on the management of post-traumatic stress disorder

SUMMARY

Post-traumatic stress disorder occurs in people exposed to life-threatening trauma. GPs may be seeing more patients with post-traumatic stress disorder as military personnel return from overseas deployments.

The condition can present in various ways. To reduce the likelihood of missed or delayed diagnosis GPs can screen at-risk populations.

A comprehensive assessment is recommended. Specialist referral may be required, particularly if there are other mental health problems.

Trauma-focused psychological therapies should be offered as the first line of treatment for post-traumatic stress disorder. Usually 8–12 sessions are needed for a therapeutic effect.

If drug treatment is needed, selective serotonin reuptake inhibitors are the first line. Other drugs used in post-traumatic stress disorder include antipsychotics, anticonvulsants and prazosin.

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Introduction

Post-traumatic stress disorder is characterised by the development of psychological and behavioural symptoms. The trauma involves exposure to death, serious injury or sexual violence. Examples of potentially traumatic events include natural disasters such as bushfires, severe accidents and assaults, as well as occupational exposures in groups such as the military and law enforcement. Post-traumatic stress disorder can be associated with high rates of comorbid depression and substance abuse. There can be significant concern about compensation, and major, long-lasting effects on families.^{1,2}

The estimated 12-month prevalence rate for post-traumatic stress disorder in the Australian community is 5.2%, compared with 8.3% in the Australian Defence Force.³ Australian GPs may encounter a new cohort of currently serving military personnel and contemporary veterans following deployments to Iraq and Afghanistan.

Clinical presentations

The typical symptoms of post-traumatic stress disorder include distressing memories of the trauma, disturbed dreams and flashbacks. The person tries to avoid things that are reminders of the trauma. They may present in a variety of ways. Some may present with the usual symptoms and have a willingness to engage in treatment. Others can present dramatically, with rapid decompensation that may include alcohol abuse, uncharacteristic anger, aggression

or violence, and sometimes deliberate self-harm. In a military setting, this may be characterised by disciplinary problems or unexpected resignation post-deployment. More subtle and gradual presentations may include increasing work problems, impaired work performance, changes in personality, social isolation and presentation with non-specific somatic complaints, in particular, insomnia.⁴ People may also present seeking assistance with a compensation claim.

Australian Vietnam War veterans with post-traumatic stress disorder are now aged in their 60s. The nature of their post-traumatic stress disorder is changing with cognitive and general health decline, becoming attenuated and generalised. This leads to presentations that do not always have classical or severe intrusive symptoms. Avoidance behaviour becomes more entrenched and habitual to the extent that it may come to be considered 'normal'. Anxiety symptoms generalise to situations that are not directly connected to the traumatic memory and may lead to intolerance of all stress.

Assessment

The presence of post-traumatic stress disorder is often missed. When patients present with repeated non-specific health problems the GP should consider asking about exposure to traumatic events. A screening tool can be helpful (Box 1).⁵ This brief screen can be supplemented by a more detailed symptom review such as the Posttraumatic Stress Disorder Checklist.⁶

Box 1 Primary care post-traumatic stress disorder screen (PC-PTSD) ⁵

'In your life, have you ever had any experience that was so frightening, horrible or upsetting that, in the past month, you:

- have had nightmares about it or thought about it when you did not want to?
- tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
- were constantly on guard, watchful, or easily startled?
- felt numb or detached from others, activities or your surroundings?

If the patient answers two or more with 'yes', a diagnosis of post-traumatic stress disorder is probable.

A formal diagnosis requires a comprehensive mental health assessment and preferably a disorder-focused interview such as the Clinician Administered Post-traumatic stress disorder Scale to improve diagnostic reliability.⁷ Post-traumatic stress disorder symptoms that persist or cause significant distress or disability require specialist referral. Ideally there should be a multidisciplinary assessment including psychiatrists, psychologists and, where relevant, nursing, social work and occupational therapy input.

When post-traumatic stress disorder becomes chronic, it is often complicated by other comorbid conditions, particularly depression, substance abuse and other anxiety disorders. Chronic pain can also be a comorbid problem when there has been both physical and psychological trauma. These comorbid conditions should also be screened for and assessed when post-traumatic stress disorder is suspected. Other related problems warranting specific assessment include suicidal ideation, anger and gambling.

Diagnostic criteria

The diagnostic criteria for post-traumatic stress disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)⁸ (Box 2) differ

from the previous edition. They have a more explicit definition of what comprises a traumatic event. Post-traumatic stress disorder is no longer included in the chapter on anxiety disorders, but is now in a new chapter, 'Trauma and stressor-related disorders'.

Treatment

Guidelines published by the Australian Centre for Post-traumatic Mental Health recommend that drugs for post-traumatic stress disorder should not be used as routine first-line treatment in preference to trauma-focused psychotherapy.⁹ The management of post-traumatic stress disorder needs to consider any comorbidities. These can influence the approach to therapy.

Psychological therapies

Trauma-focused psychological treatments are the most effective evidence-based interventions for post-traumatic stress disorder.⁹ These include trauma-focused cognitive behavioural therapy that can involve prolonged exposure and cognitive processing therapy, or eye movement desensitisation and reprocessing. Second-line psychological treatments that are not trauma-focused, but can be helpful, include stress inoculation training.

Typically, 8–12 trauma-focused therapy sessions of 90 minutes duration are required to produce the best therapeutic effects. This treatment is frequently demanding and logistically difficult, so there is considerable interest in recent work on an intensive two-week version.¹⁰

As GPs will usually have the central coordinating and referral role, it is important for them to be aware that their patient is receiving evidence-based treatment. Long-term supportive counselling is often appreciated by patients, however this approach is unlikely to have a positive impact.

The trauma-focused therapies will, by their nature, involve increasing the patient's level of anxiety and

Box 2 DSM-5 criteria for post-traumatic stress disorder ⁸

The following diagnostic criteria apply to adults, adolescents, and children older than six years:

- exposure to actual or threatened death, serious injury, or sexual violence
- presence of one (or more) intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred
- persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred
- negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred
- marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred
- duration of the disturbance is more than one month
- the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- the disturbance is not attributable to the physiological effects of a substance (e.g. drug, alcohol) or another medical condition

Adapted from DSM-5 criteria for PTSD ⁸

distress. This occurs in a safe and contained manner, the patient is taught strategies to manage this arousal, and the levels of distress drop to manageable levels by the end of the session. It is vital that avoidance mechanisms and behaviours that are core symptoms of post-traumatic stress disorder are made overt and explicitly addressed in the therapy.

Drug treatment

Drug therapy may be used when⁹:

- patients are unwilling or not in a position to engage in psychotherapy
- patients have a serious comorbid condition or associated symptoms, for example severe depression
- patients' circumstances are not sufficiently stable to commence trauma-focused psychotherapy, for example high risk of suicide or harm to others
- the severity of patient distress cannot be managed by psychological means alone
- there has been an insufficient response to psychotherapy alone
- there is a past history of a positive response to medication.

When drugs are used, the patient's mental state needs to be reviewed regularly with a view to starting psychotherapy when appropriate.

Antidepressants

Selective serotonin reuptake inhibitors are the first choice of drug. This advice is based on an extensive review of the evidence for the Australian guidelines (2013),⁹ and on other meta-analyses.¹¹ The Australian guidelines found insufficient evidence to warrant recommending one selective serotonin reuptake inhibitor over another.

With respect to dosing, patients with post-traumatic stress disorder may be very aware of their somatic reactions, such as nausea or headache. It is therefore important to 'start low, go slow, aim high' to minimise initial adverse effects and to achieve doses that are more likely to be effective.¹² When symptoms have failed to respond to a particular drug, consideration should be given to increasing the dose within approved limits.⁹ The Australian guidelines recommend that patients with post-traumatic stress disorder who have responded to drug treatment should continue on the dose that achieved remission for at least 12 months before gradual withdrawal is attempted.⁹

Patients who respond to antidepressant drugs usually show some improvement within the first two weeks of treatment with an adequate dose. If there is no response, then consultation with a psychiatrist is

advised and consideration should be given to changing to another class of antidepressant. Specifically, if a patient has not responded to an adequate trial of a selective serotonin reuptake inhibitor, then either another selective serotonin reuptake inhibitor or a serotonin noradrenaline reuptake inhibitor should be tried, after a suitable withdrawal and washout period. If the patient still does not respond, then switching to a different class of antidepressant is advised. Further trials of either mirtazapine, moclobemide, a tricyclic antidepressant or an irreversible monoamine inhibitor could be considered, if required.¹³

Benzodiazepines

In the absence of any evidence of benefit, the Australian guidelines do not mention benzodiazepines specifically. They recommend that 'appropriate sleep medication' should only be used cautiously and then only in the short term (for less than one month continuously) in those patients who have not responded to non-drug interventions.⁹ Both the US¹³ and Australian⁹ guidelines highlight the common problems of misuse, tolerance and dependency in patients taking benzodiazepines.

Antipsychotics

The use of antipsychotic drugs for post-traumatic stress disorder is not well supported by research evidence. When there is an inadequate symptom response to other drugs, the Australian guidelines recommend a specialist opinion to determine the appropriateness of using olanzapine or risperidone as augmentation strategies.¹⁰ Anecdotal experience suggests that this class of medication can, in individuals with more severe and complex post-traumatic stress disorder, improve nightmares, insomnia, mood, anxiety, anger and dissociation. Despite the lack of evidence, many clinicians prefer quetiapine to olanzapine and risperidone as an augmentation strategy, as it is less likely to cause metabolic or extrapyramidal adverse effects.

If atypical antipsychotics are used, metabolic monitoring should be undertaken and documented. This should include regular monitoring of blood pressure, waist measurement, body weight, lipids and fasting glucose.

Anticonvulsants

The Australian guidelines do not make specific recommendations about the use of anticonvulsants for post-traumatic stress disorder. The US guidelines advise against their use, especially valproate, topiramate and tiagabine, as monotherapy. They also concluded that there was insufficient evidence to recommend an anticonvulsant as an adjunctive treatment.

The likely clinical scenario that leads to consideration of using an anticonvulsant in the treatment of post-

ARTICLE

Post-traumatic stress disorder

traumatic stress disorder is when the presentation is characterised by treatment resistance, severity and complexity. Certain presenting symptoms such as anger, impulsivity and dissociation can be targeted with anticonvulsants, but the same precautions regarding risk and benefit as outlined for benzodiazepines are recommended.

Prazosin

Prazosin, an alpha₁ adrenoreceptor antagonist, has yielded mixed results in the treatment for post-traumatic stress disorder. However, it has shown consistent efficacy in improving sleep and reducing nightmares. As prazosin can cross the blood-brain barrier it may dampen the noradrenergic activity thought to contribute to nightmares. Both the US and the Australian guidelines⁹ recommend prazosin as an adjunctive treatment. A subsequent study confirmed its effectiveness with sleep symptoms and found prazosin was effective for overall post-traumatic stress disorder symptoms in a study over 15 weeks.¹⁴ Mean achieved total daily doses of 19.6 mg for males and 8.7 mg for females were well tolerated. Postural hypotension, headache, dry mouth and fatigue are among the reported adverse effects.

There are no evidence-based recommendations for how long prazosin should be used in the treatment of post-traumatic stress disorder. We recommend that when used, its efficacy and tolerability be regularly reviewed, and when there is clear clinical evidence for ongoing benefit it should be continued.

Referral and patient support

Consultation with a psychiatrist is recommended when:

- diagnostic clarification is required
- comorbid conditions are present
- post-traumatic stress disorder is severe or complex with concern about patient safety
- there is treatment resistance requiring consideration of augmentation strategies, polypharmacy or the use of irreversible monoamine inhibitors.

Support and self-help groups are available for post-traumatic stress disorder sufferers who are veterans, ranging from traditional ex-service organisations such as the Returned and Services League (RSL) through to self-help organisations such as 'Soldier On'. Veterans and their families also have free access to the Veterans and Veterans Families Counselling Service. Other groups of trauma victims are less well served. The network of Centres Against Sexual Assault provide counselling services for survivors of sexual trauma. Following natural disasters such as the Black Saturday bushfires, communities often draw together to provide important social and practical support for each other. It is important for GPs to be aware of these services and opportunities and the benefits they afford patients with post-traumatic stress disorder.

There is an increasing number of online education and resource sites for GPs that can assist in their skills development in this area (see Box 3).

Conclusion

Post-traumatic stress disorder is a common mental health disorder that can cause severe distress and disability. It is frequently underdiagnosed so screening for it could improve detection. There is a growing body of clinical research that has led to treatment guidelines that consistently recommend trauma-focused psychological therapies as the most effective first-line treatment. When pharmacotherapy is required selective serotonin reuptake inhibitors should be used first. ◀

Duncan Wallace is a member of the Australian Centre for Posttraumatic Mental Health Multidisciplinary Panel that developed the Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder (2013).

John Cooper is a staff member at the Australian Centre for Posttraumatic Mental Health where the Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder (2013) were developed.

**SELF-TEST QUESTIONS***True or false?*

1. Prazosin may improve the sleep of patients with post-traumatic stress disorder.
2. Tricyclic antidepressants are the drugs of first choice for treating post-traumatic stress disorder.

Answers on page 71

Box 3 Online education and resources for GPs

Royal Australian College of General Practitioners
Six-hour GPelearning activity module: Managing disaster and trauma-related mental health problems. 2014.
www.racgp.org.au/education/courses/activitylist/activity/?id=131&q=keywords%3dtrauma

Department of Veterans' Affairs
At Ease Portal. Mental Health Advice Book. Part 2, Chapter 6. Posttraumatic stress disorder. 2012.
<http://at-ease.dva.gov.au/professionals/mental-health-advice-book/part-2-advice-for-general-practitioners/6-posttraumatic-stress-disorder-gp-summary/>

REFERENCES

1. Westerink J, Giarratano L. The impact of posttraumatic stress disorder on partners and children of Australian Vietnam veterans. *Aust N Z J Psychiatry* 1999;33:841-7.
2. Morbidity of Vietnam veterans: suicide in Vietnam veterans' children. Supplementary report no. 1. Canberra: Australian Institute of Health and Welfare; 2000.
3. McFarlane AC, Hodson SE, Van Hooff M, Davies C. Mental health in the Australian Defence Force: 2010 ADF Mental Health and Wellbeing Study: Full report. Canberra: Department of Defence; 2011.
4. Coetzee RH, Simpson RG, Greenberg N. Detecting post-deployment mental health problems in primary care. *J R Army Med Corps* 2010;156:196-9.
5. Prins A, Ouimette P, Kimerling R, Cameron RP, Hugelshofer DS, Shaw-Hegwer J, et al. The primary care PTSD screen (PC-PTSD): development and operating characteristics. *Prim Care Psychiatry* 2003;9:9-14.
6. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5). Washington, DC: U.S. Department of Veterans Affairs, National Center for PTSD; 2013. www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp [cited 2015 Mar 3]
7. Large MM, Nielssen O. Improving the reliability of the diagnosis of post-traumatic stress disorder in civil litigation. *Psychiatry, Psychology and Law* 2010;17:79-87.
8. American Psychiatric Association. DSM-5 criteria for PTSD. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. Arlington, VA: American Psychiatric Association; 2013. www.ptsd.va.gov/professional/PTSD-overview/dsm5_criteria_ptsd.asp [cited 2015 Mar 3]
9. Australian guidelines for the treatment of acute stress disorder and posttraumatic stress disorder. Melbourne: Australian Centre for Posttraumatic Mental Health; 2013.
10. Blount TH. Intensive outpatient prolonged exposure for combat-related PTSD: a case study. *Cognitive Behav Pract* 2014;21:89-96.
11. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev* 2006. CD002795.
12. Schaffer A, McIntosh D, Goldstein BI, Rector NA, McIntyre RS, Beaulieu S, et al. The CANMAT task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. *Ann Clin Psychiatry* 2012;24:6-22.
13. Veterans Affairs/Department of Defense. Clinical practice guidelines: Management of posttraumatic stress. Washington, DC: U.S. Department of Veterans Affairs and Department of Defense; 2010.
14. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry* 2013;170:1003-10.

Book review

Martindale: The Complete Drug Reference. 38th ed.

London: Pharmaceutical Press; 2014
4109 pages

Also available online www.medicinescomplete.com

This book is presented as a hefty two volume set housed in a simple outer case. My first impression of this edition is that it is extremely heavy (about 6 kg) and has a large footprint, so make sure it's kept on a low shelf!

There have been significant changes in the presentation of information since the 37th edition. Volume A consists of monographs covering a wide range of drug classes as well as sections on pesticides and repellents, radiopharmaceuticals and sex hormones and their modulators. The section 'Vaccines, immunoglobulins and antisera' contains a wealth of information on the effects of vaccines on a patient's organs. Volume B contains a list of selected preparations, manufacturers, pharmaceutical terms and indexes.

The drug monographs are laid out in an easy-to-read manner and have been restructured. 'Uses and administration' appears immediately after the physicochemical description of the substance. In contrast to other references such as Micromedex and

MIMS, the pharmacokinetic information for products appears at the end of the monograph, after the interactions and adverse effects.

The information is current and well researched, although there were some gaps in entries, especially with respect to complementary and alternative therapies. The location of these products was also confusing, with some like milk thistle listed under 'Chelators, antidotes and antagonists' and others like garlic included in 'Miscellaneous drugs and other substances'.

The most obvious change to the drug monographs is the deletion of the chemical structure diagrams in the print version. This has allowed for a restructure of the monographs using larger font size to increase readability. Unfortunately, this deletion has removed the ability to quickly compare the structures of substances. This was useful when trying to ascertain whether structurally based cross-reactivity between drugs may exist. The disclaimer that this information is available in the electronic form of Martindale is provided in the preface to this edition and begs the question 'Is the print version still relevant?'.

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Treatment for Alzheimer's disease: has anything changed?

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Key words

Alzheimer's disease,
cholinesterase inhibitors,
dementia, memantine

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SUMMARY

Current therapies for Alzheimer's disease do not modify the course of disease and are not universally beneficial.

Clinical trials of drugs targeting amyloid and tau in established Alzheimer's disease have been unsuccessful as it is thought that treating established disease may be too late.

Research has moved to the prodromal and pre-symptomatic phases of Alzheimer's disease, with a greater emphasis on the role of biomarkers in defining cases and monitoring response to therapy.

Mixed pathologies predominate in the older population. The associations between biomarkers, neuropathology and clinical syndromes are weaker in older people and this is likely to pose a greater challenge in identifying effective therapies.

Introduction

Alzheimer's disease is the most prevalent of the dementias. There are no disease-modifying therapies and the condition is progressive, significantly impacting on cognition, function, lifespan and healthcare use. Any pharmacological management must be done in tandem with optimising the management of comorbidities, including behavioural symptoms, rationalising other medicines, and ensuring adequate education, carer support and provision of services.

Current therapies

There have been many unsuccessful therapeutic trials in Alzheimer's disease. Failed therapies include anti-inflammatories, statins, hormonal therapies and chelators (drugs that bind metals that are thought to promote abnormal amyloid beta aggregation).

Cholinesterase inhibitors

Cholinergic neurotransmitter activity is low in Alzheimer's disease. Cholinesterase inhibitors are thought to work by reducing the breakdown of the neurotransmitter acetylcholine. Donepezil, galantamine and rivastigmine are currently approved for use in mild to moderate Alzheimer's disease, with rivastigmine also available as a transdermal patch. The three are equally efficacious and may temporarily improve cognition.

Pooled trials of cholinesterase inhibitors identified an improvement of 1.4 points on a Mini-Mental State Examination (MMSE) over six months. Small but statistically significant improvements in activities of daily living and behavioural symptoms, such as apathy, have also been identified. However, these

improvements represent an average from thousands of trial participants, with individual responses varying.¹ Only one-third of people show a clinically measurable benefit. Another third show clinical worsening during the first six months of therapy, and drop-out rates of 29% due to adverse effects are observed. The common adverse effects associated with cholinesterase inhibitors include nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, muscle cramps, insomnia and nightmares. Relative contraindications to their use include heart block, bradyarrhythmias, epilepsy, active peptic ulcer disease, obstructive urinary disease and significant airway disease.

Cost-benefit studies of cholinesterase inhibitors, although limited, have failed to identify any economic benefit. There are no randomised double-blind placebo controlled trials showing that cholinesterase inhibitors delay entry into residential care. Weak evidence suggesting a delay is from less robust open-label studies and extrapolation of data from short-term trials. Although cholinesterase inhibitors are the current mainstay of Alzheimer's disease therapy, objective and measurable benefit is not seen in most patients. These drugs do not modify disease and their economic benefits are uncertain.

Memantine

Memantine is a glutaminergic N-methyl-D-aspartate (NMDA) receptor antagonist currently thought to reduce NMDA receptor-mediated neurotoxicity. It is approved for moderate to severe Alzheimer's disease. Memantine has a statistically significant effect on cognition, behaviour and the ability to perform activities of daily living.² A small reduction in agitation

has been consistently observed. However, the trials examining memantine were limited by high drop-out rates, and the benefits identified, although statistically significant, were of small magnitude. A recent two-year trial has provided further evidence that memantine does not modify disease progression and is ineffective in mild Alzheimer's disease.³

Data showing an economic benefit are limited. Given the small clinical benefits and the lack of effect on progression, memantine, like the cholinesterase inhibitors, provides symptomatic relief to some but has failed to provide universal benefit in Alzheimer's disease.

Alternative therapies

Souvenaid is a nutritional supplement which combines vitamins and lipids. In two positive phase II trials of 12 and 24 weeks' duration in people with mild Alzheimer's disease (MMSE ≥ 20), the supplement was given to people not taking a cholinesterase inhibitor. The 12-week study found a statistically significant benefit on a delayed verbal recall task but no benefit on other cognitive, behavioural or functional measures. In the 24-week trial, the Neuropsychological Test battery failed to show any statistically significant improvement. However, when the memory test sub-score within the battery was examined, there was a statistically significant benefit that was predominantly driven by improvements between weeks 12 and 24 of the study.

In a third 24-week study of mild to moderate Alzheimer's disease (MMSE 14–24), Souvenaid was used in combination with either a cholinesterase inhibitor, memantine or both. No evidence for cognitive or functional benefit was found.

In all three studies, the supplement was well tolerated but there was no evidence that Souvenaid slowed

cognitive or functional decline. However, it may improve memory in the early stages of the disease in those who have not previously taken cholinesterase inhibitors.⁴ The potential small benefits need to be balanced with the cost of therapy – approximately \$4 daily.

Numerous complementary and alternative medicines are used by patients with Alzheimer's disease, including *Ginkgo biloba*, acetyl-L-carnitine, curcumin and coconut oil. Although many of these compounds are associated with plausible hypothetical effects and encouraging results from basic research, randomised trial data have not confirmed their benefit.

Therapeutic directions

Current research is focusing on drugs that may slow or prevent disease progression (Table). Neurodegenerative conditions such as Alzheimer's disease are thought to be proteinopathies. These are diseases caused by the deposition of abnormally folded or processed proteins that lead to cell death. Factors including inflammation, excitotoxicity (excessive release of stimulatory neurotransmitters resulting in neuronal death), mitochondrial dysfunction and free radical damage, perhaps induced by these proteins, are thought to promote the neurodegenerative process.

Alzheimer's disease is characterised by the deposition of two proteins – amyloid-beta which is the predominant component of plaques, and hyperphosphorylated tau. Measuring the concentrations of these proteins in the brain and cerebrospinal fluid through labeled positron emission tomography (PET) and quantitative assessment is now possible and has become an integral component of therapeutic trials.

Table Therapeutic strategies in the treatment of Alzheimer's disease

Target	Strategies
Amyloid	Decreasing amyloid-beta production: beta and gamma secretase inhibitors, alpha secretase promoters Amyloid removal Active immunisation with vaccines Passive immunisation with specific antibodies, intravenous gamma globulin Blocking amyloid-beta signalling Inhibition of amyloid-beta aggregation
Tau	Inhibition of phosphorylation Active immunisation Prevention of aggregation
Other	Insulin sensitisation e.g. intranasal insulin Growth factors Anti-ageing e.g. resveratrol

Proteinopathy-based therapies in established Alzheimer's disease

Anti-amyloid drugs

The autosomal dominant forms of Alzheimer's disease are caused by mutations that result in abnormal amyloid precursor protein processing and deposition. These findings have given rise to the amyloid cascade hypothesis which postulates that the transmembrane protein, amyloid precursor protein, is abnormally cleaved by beta and gamma secretase enzymes. This results in an over-production of amyloid-beta peptides that aggregate to ultimately form the characteristic amyloid plaques of Alzheimer's disease. The abnormal amyloid-beta fragments are thought to be toxic, promoting the neurodegenerative process.

Anti-amyloid drugs aim to either decrease amyloid-beta production, increase its clearance or reduce aggregation of the protein. Amyloid-beta production can be inhibited by modifying the activity of the beta and gamma secretase enzymes that cleave the amyloid precursor protein. Despite evidence of efficacy for these drugs in vitro and in mice, drugs that inhibit the beta and gamma secretases have failed to show any benefit in established disease in clinical trials.

Immunotherapy has been used to increase clearance of amyloid-beta through active (vaccination) or passive (monoclonal antibodies, gamma globulin) immunisation. Initial vaccination trials were ceased due to meningoencephalitis, with no cognitive benefit found. Results are awaited from a phase II trial of a new vaccine.

Passive immunotherapy is based on the administration of monoclonal or polyclonal antibodies against amyloid-beta. Recently published phase III trials of two monoclonal antibodies have failed to show any benefit, with vasogenic oedema and microhaemorrhages identified as a potentially serious adverse event.⁵ Intravenous immunoglobulins have also failed to show benefit. Of the limited trials of drugs that inhibit the aggregation of amyloid, none have been positive to date.

Anti-tau drugs

The amyloid hypothesis has dominated much of the research into effective therapies for Alzheimer's disease. However, recent failures for amyloid-based therapies have led some to question whether amyloid-beta is the consequence rather than the cause of Alzheimer's disease.

Tau is a protein that stabilises microtubules. It is abundant in neurons but in Alzheimer's disease it is hyperphosphorylated in the form of tangles.

Anti-tau therapies have focused on inhibition of tau aggregation and phosphorylation. Trials of anti-tau therapies in established Alzheimer's disease have not yet been successful.

Other drugs

There are numerous other drugs currently being trialled in established Alzheimer's disease including intranasal insulin and resveratrol. Resveratrol stimulates the sirtuin pathway. Sirtuin proteins are thought to have an anti-ageing effect and have been found to promote the activity of alpha secretase. In contrast to beta and gamma secretase, alpha secretase cleaves the amyloid precursor protein into peptides that do not aggregate. Promoting alpha secretase through the sirtuin pathway may potentially reduce the formation of amyloid plaques. A phase II trial of a gene therapy, which is thought to stimulate nerve growth factor, is currently in progress.

Current research directions

In trials to date, treatment of mild to moderate Alzheimer's disease with anti-amyloid therapies has resulted in the removal of amyloid, but the cognitive deficits of the disease have persisted. The current hypothesis is that anti-amyloid therapy is too late once there is established dementia as it is known that amyloid deposits precede cognitive changes by 10–15 years. Trials have therefore shifted to what is believed to be the two precursor states of Alzheimer's disease. The prodromal phase, termed prodromal Alzheimer's disease or mild cognitive impairment, is characterised by mild cognitive deficits in the absence of dementia with or without biomarker positivity. The hypothesised earliest phase of Alzheimer's disease is called pre-symptomatic Alzheimer's disease and is characterised by intact cognition in association with amyloid deposition as detected by biomarkers or a known genetic inheritance.

Trials in prodromal (or mild cognitive impairment) and pre-symptomatic Alzheimer's disease are in progress with amyloid being the major target. Trials in pre-symptomatic Alzheimer's disease are using monoclonal drugs targeting amyloid⁶ and include:

- A4 study (Anti-Amyloid Treatment in Asymptomatic Alzheimer's) in cognitively normal 65–85 year olds who have abnormal amyloid deposition as determined by PET scans
- Dominantly Inherited Alzheimer's Network study in pre-symptomatic individuals with dominantly inherited Alzheimer's disease
- Alzheimer's Prevention Initiative in a large familial cohort with a known autosomal dominant Alzheimer's disease mutation.

These studies will be vital for understanding the role of amyloid in Alzheimer's disease pathogenesis. The A4 study will shed light on whether late onset sporadic Alzheimer's disease behaves in a biologically similar way to inherited early onset Alzheimer's disease.

Cautions and challenges for the future

Many believe that a single modality for treating Alzheimer's disease will not be possible and that future therapies will need to address multiple aspects in the pathogenesis of Alzheimer's disease. A major issue facing trials is the convergence of symptoms that may occur within the dementia spectrum.

Dementias with the same clinical features may in fact be caused by different pathologies. Although biomarker studies may assist in identifying the associated proteinopathy, to date these studies have focused on well-defined and evaluated clinic-based populations. It is unknown how this will extrapolate to patients in the community where mixed pathologies may predominate.

One of the greatest future challenges lies in the epidemiology of Alzheimer's disease. Age is the strongest predictor of disease and significantly outweighs all other risk factors and biomarkers. Older people suffer from more medical comorbidities. They have higher rates of sensory loss, psychoactive medicine use and frailty. These factors can have a significant impact on cognition, leading some to postulate that dementia in the 'old-old' also reflects these multiple coexistent pathologies. Amyloid scans are positive in about 65% of people over the age of 80, but are not predictive of cognitive function.

REFERENCES

1. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006. CD005593.
2. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev 2006. CD003154.
3. Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA co-operative randomized trial. JAMA 2014;311:33-44.
4. NPS MedicineWise. 2014. Souvenaid: Help for people with Alzheimer's disease? www.nps.org.au/publications/health-professional/health-news-evidence/2014/souvenaid [cited 2015 Mar 3]
5. Karran R, Hardy J. Anti-amyloid therapy for Alzheimer's disease - are we on the right road? N Engl J Med 2014;370:377-8.
6. Friedrich MJ. Researchers test strategies to prevent Alzheimer disease. JAMA 2014;311:1596-8.

Neuropathological post-mortem studies of brains have identified that in those aged over 85, the prevalence of pathological Alzheimer's disease is similar between people with and without dementia, and about half of those over 90 with clinical dementia do not have sufficient neuropathology to account for their dementia. Therefore, although phenotypically similar to younger sufferers, older people suffer from a greater diversity of pathologies and it seems far less likely that they will respond in a uniform manner to proteinopathy-based therapies.

Conclusion

Currently available treatments provide symptomatic relief for Alzheimer's disease but the benefits are not universal. The recent history of drug trials in Alzheimer's disease suggests that a cautious approach in announcing a 'cure' is prudent. The inability to translate results from in vitro and animal studies to success in human trials has beset Alzheimer's disease research and reflects the complexity of the disease pathogenesis. A large number of therapies with a plausible scientific basis and positive phase II trials have failed when progressed to phase III trials.

Proteinopathy-based therapies in established Alzheimer's disease have failed and studies are now focusing on pre-symptomatic individuals as defined by biomarkers or genetic inheritance. Should these trials be successful, screening, escalating healthcare costs and translation to older dementia sufferers are likely to create new challenges. <

Conflict of interest: none declared

New drugs

Empagliflozin

Approved indication: type 2 diabetes

Jardiance (Boehringer Ingelheim)

10 mg and 25 mg film-coated tablets

Australian Medicines Handbook section 10.1.5

Empagliflozin is the third inhibitor of the sodium-glucose co-transporter 2 (see Aust Prescr 2014;37:14-16 and 2014;37:17-20) to be approved for the treatment of adults with type 2 diabetes. Canagliflozin and dapagliflozin are already available in Australia. By inhibiting renal reabsorption of glucose, the drugs increase glucose excretion thereby decreasing blood glucose.

Empagliflozin is rapidly absorbed and there is an immediate increase in the excretion of glucose which continues for at least 24 hours. The elimination half-life is approximately 12 hours with excretion in urine and faeces. There is some metabolism, but this does not involve the cytochrome P450 system. Empagliflozin is a substrate for the P-glycoprotein transporter, but it is unlikely that it will cause interactions with other

substrates. Renal and hepatic impairment will increase plasma concentrations of empagliflozin, but no dose adjustment is recommended. However, empagliflozin is contraindicated if the eGFR is 45 mL/min/1.73 m² or less.

A phase III placebo-controlled trial randomised 899 previously untreated patients to take once-daily empagliflozin 10 mg or 25 mg or sitagliptin 100 mg. These patients had a mean HbA1c of 63 mmol/mol (7.88%). After 24 weeks this had been significantly reduced by the active treatments (see Table 1). The proportion of patients achieving a concentration below 53 mmol/mol (7%) was 12% with placebo, 35% with empagliflozin 10 mg, 44% with 25 mg and 38% with sitagliptin. Patients taking empagliflozin 10 mg lost 2.26 kg in weight and those taking 25 mg lost 2.48 kg while there was no significant weight loss with placebo or sitagliptin.¹

Like other sodium-glucose co-transporter 2 inhibitors, empagliflozin has also been studied in combination with other drugs for diabetes (see Table 1). It is most likely to be used in this way, unless the patient has an intolerance of metformin.

Table 1 Effect of once-daily empagliflozin on glycated haemoglobin (HbA1c)

Trial	Duration	Treatment	Mean change in HbA1c (%) from baseline
Roden et al ¹ (monotherapy)	24 weeks	placebo	+0.08
		empagliflozin 10 mg	-0.66
		empagliflozin 25 mg	-0.78
		sitagliptin 100 mg	-0.66
Häring et al ²	24 weeks	metformin plus	
		placebo	-0.13
		empagliflozin 10 mg	-0.70
		empagliflozin 25 mg	-0.77
Rosenstock et al ³	12 weeks	metformin plus	
		placebo	+0.15
		empagliflozin 10 mg	-0.56
		empagliflozin 25 mg	-0.55
		sitagliptin 100 mg	-0.45
Ridderstråle et al ⁴	104 weeks	metformin plus	
		empagliflozin 25 mg	-0.66
		glimepiride 1-4 mg	-0.55
Häring et al ⁵	24 weeks	metformin and sulfonylurea plus	
		placebo	-0.17
		empagliflozin 10 mg	-0.82
		empagliflozin 25 mg	-0.77



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.

Empagliflozin was added to the treatment of patients who had a mean HbA1c of at least 53 mmol/mol (7%) despite treatment with metformin. A placebo was given to 207 patients, while 217 added empagliflozin 10 mg and 213 added empagliflozin 25 mg. After 24 weeks the mean HbA1c fell by 1.4 mmol/mol with placebo, 7.7 mmol/mol with empagliflozin 10 mg and by 8.4 mmol/mol with 25 mg. In percentage units, the difference from placebo was 0.57% with empagliflozin 10 mg and 0.64% with empagliflozin 25 mg.²

In another study of patients with diabetes that was not completely controlled by metformin, 495 were randomised to add either empagliflozin 1 mg, 5 mg, 10 mg, 25 mg or 50 mg, or a placebo or open-label sitagliptin 100 mg daily. Apart from the 1 mg dose, all the active treatments produced a significant reduction in HbA1c by 12 weeks. Adding empagliflozin 10 mg reduced the mean HbA1c from 63 mmol/mol (7.9%) to approximately 57 mmol/mol (7.34%). The proportion of patients achieving an HbA1c of 53 mmol/mol (7%) or less was 15.5% with placebo, 38% with empagliflozin 10 mg and 33.8% with sitagliptin. Body weight reduced by 1.2 kg in the control group and by 2.7 kg with 10 mg empagliflozin.³

Another study compared empagliflozin with glimepiride in patients with diabetes that was inadequately controlled by diet, exercise and metformin. The mean HbA1c at baseline was 63 mmol/mol (7.92%) in the 769 patients randomised to add empagliflozin and in the 780 randomised to add glimepiride. After 104 weeks the mean reduction in HbA1c was 0.66% with empagliflozin and 0.55% with glimepiride. This showed that the effect of empagliflozin was statistically superior to glimepiride. Empagliflozin also reduced weight and blood pressure.⁴

Empagliflozin has also been studied in patients with diabetes that was not well controlled by metformin and a sulfonylurea. In one trial 669 patients were randomised to add empagliflozin 10 mg, 25 mg or a placebo to their regimen. After 24 weeks the HbA1c concentration had been significantly reduced by empagliflozin. Expressed as percentage units, the

reductions were 0.82% with 10 mg, 0.77% with 25 mg and 0.17% with placebo. At the start of the study the mean HbA1c was 65 mmol/mol (8.1%). While 9.3% of the patients in the placebo group achieved a concentration below 53 mmol/mol (7%), this was reached by 26.3% of the empagliflozin 10 mg group and 32.2% of the 25 mg group. There was a weight loss of 2.16 kg with empagliflozin 10 mg and 2.39 kg with 25 mg, compared with 0.39 kg in the placebo group.⁵

A study of empagliflozin as an add-on to basal insulin found significant reductions in HbA1c over 78 weeks. In the group of 169 patients who added 10 mg empagliflozin the HbA1c fell by 0.48% from a baseline of 8.26% (67 mmol/mol), while in the 170 patients who added a placebo it fell by 0.02% from a baseline of 8.1% (65 mmol/mol).⁶

There has been a systematic review of 10 studies of empagliflozin involving 6203 people. The results suggest that empagliflozin 25 mg has similar effects on HbA1c as metformin and sitagliptin. It also reduces weight and blood pressure (see Table 2).⁷

Although empagliflozin increases the amount of glucose in the urine, the increase in urinary tract infections was not significantly different from placebo in the systematic review.⁷ However, a different pooled analysis did find a significant increase. There is also a significant increase in genital tract infections compared with placebo.⁷ The osmotic diuresis caused by glucose can lead to volume depletion and decreased renal function.

While the incidence of hypoglycaemia is no different from placebo with monotherapy it rises when empagliflozin is combined with other treatments.⁷ When combined with metformin and a sulfonylurea, the incidence of hypoglycaemia was 16.1% with empagliflozin 10 mg and 11.5% with 25 mg daily.⁵

In combination with insulin it was 19.5% with empagliflozin 10 mg and 28.4% with 25 mg daily.

Due to a lack of data, empagliflozin is not recommended for children or during pregnancy and lactation.

Prescribers now have a variety of drugs to consider when a patient's type 2 diabetes cannot be controlled

Table 2 Meta-analysis of ten trials of empagliflozin for type 2 diabetes⁷

Outcome measure	Outcome for empagliflozin compared to placebo	
	10 mg once daily	25 mg once daily
Change in glycated haemoglobin (HbA1c)	-0.62%	-0.66%
Odds ratio for patients achieving HbA1c below 53 mmol/mol (7%)	3.83	4.4
Change in weight	-1.85 kg	-1.84 kg
Change in systolic blood pressure	-3.49 mmHg	-4.19 mmHg
Change in diastolic blood pressure	-1.28 mmHg	-1.88 mmHg

NEW DRUGS

by diet, exercise and metformin. If the prescriber adds a sodium-glucose co-transporter 2 inhibitor there is also a choice of drugs. All the members of the class reduce HbA1c and body weight, but increase the risk of genitourinary infection. There has been a concern about a possible higher risk of cancer in patients taking dapagliflozin, but it is too early to say if there will be a similar concern with empagliflozin. Although empagliflozin reduces the concentration of HbA1c, it is also too early to know the drug's effect on clinical outcomes.

T manufacturer provided the product information

REFERENCES *†

1. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2013;1:208-19.
2. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, et al; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2014;37:1650-9.
3. Rosenstock J, Sernan LJ, Jelaska A, Hantel S, Pinnett S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes Obes Metab* 2013;15:1154-60.
4. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG H2H-SU trial investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol* 2014;2:691-700.
5. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, et al; EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2013;36:3396-404.
6. Rosenstock J, Jelaska A, Wang F, Kim G, Broedl U, Woerle HJ, et al. Empagliflozin as add on to basal insulin for 78 weeks improves glycemic control with weight loss in insulin-treated type 2 diabetes (T2DM). *Can J Diabetes* 2013;37 Suppl 4:S32.
7. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2014;16:984-93.

First published online 13 February 2015

Perampanel

Approved indication: epilepsy

Fycompa (Eisai)

2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg film-coated tablets

Australian Medicines Handbook section 16.1.3

Carbamazepine is considered to be the first-line treatment for partial-onset seizures. If it does not completely control the seizures there are several drugs which can be considered for adjunctive treatment. Perampanel adds to these options.

Glutamate is an excitatory neurotransmitter in the brain which may trigger seizures. Perampanel is a non-competitive antagonist at one of the glutamate receptors. By binding to the post-synaptic AMPA-glutamate receptor, perampanel is thought to reduce glutamate-induced neurotransmission.

Treatment begins with 2 mg at bedtime and is gradually increased according to the clinical response. Perampanel is completely absorbed. There is extensive metabolism which includes cytochrome P450 3A. This means that there is a potential for interactions with inducers and inhibitors of this enzyme system. As carbamazepine is an enzyme inducer it will lower plasma concentrations of perampanel and patients may need a higher dose of perampanel. The metabolites are excreted in the urine and faeces. The mean half-life of perampanel is 105 hours. Dose titration should only be done at a minimum of two-weekly intervals, unless the patient is taking a drug, such as carbamazepine, that shortens the half-life of perampanel. Lower doses may be needed in patients with liver disease and perampanel is not recommended for patients with severe hepatic impairment or moderate and severe renal impairment.

The efficacy of perampanel was studied in three main trials involving patients with a minimum age of 12 years. They were experiencing partial seizures, with or without secondary generalised seizures, despite treatment with up to three antiepileptic drugs. After a baseline period of six weeks 1480 patients were randomised to add perampanel or a placebo. There was then a six-week titration phase followed by maintenance treatment for 13 weeks. The target doses of perampanel were 2 mg, 4 mg and 8 mg in one trial and 8 mg and 12 mg in the other two trials.¹⁻³

The median frequency of partial seizures at the start of the trials was 10-13 per 28 days. Pooled analysis of the three trials showed that perampanel reduced seizure frequency.⁴ The median percentage reduction in the frequency of partial seizures was 23.3% with 4 mg, 28.8% with 8 mg and 27.2% with 12 mg. These changes were significantly greater than the 12.8% reduction in the placebo group. There were also reductions in secondary generalised seizures, and a 50% reduction in seizure frequency was achieved by significantly more patients in the perampanel groups (see Table).

During the trials adverse events affected 77% of the perampanel groups and 66.5% of the placebo group. Symptoms which were more frequent with perampanel included dizziness, somnolence and fatigue. Adverse reactions resulted in the withdrawal of 4.8% of the patients taking placebo. In the perampanel groups the withdrawal rates were 3% with 4 mg, 8% with 8 mg

Table Pooled efficacy data from phase III trials of perampanel¹⁻⁴

	Daily dose of perampanel			
	Placebo	4 mg	8 mg	12 mg
Number of patients	442	172	431	255
Monthly frequency of partial seizures at baseline	11.1	10	12.2	13
Median change in partial seizures after treatment	-12.8%	-23.3%	-28.8%	-27.2%
Monthly frequency of secondary generalised seizures at baseline	3.7	3.7	3.4	4.1
Median change in secondary generalised seizures after treatment	-19.4%	-48.6%	-62.9%	-53.3%
Proportion of patients with >50% reduction in partial seizures	19.3%	28.5%	35.3%	35%
Proportion of patients who became seizure-free after treatment	1%	4.3%	3.3%	3.7%

and 19% with 12 mg. Some patients withdrew because of ataxia. Altered gait, balance disorder and falls were also reported. This could potentially be more of a problem in elderly patients, but the elderly were not well represented in the trials.

During the trials a weight gain of more than 7% body weight was more common in patients taking perampanel than those taking placebo (14.6% vs 7.1%).⁴ Parampanel may provoke psychiatric problems. Some patients become angry and aggressive. Hostility and aggression were reported in 20% of the patients taking perampanel 12 mg daily versus 6% of the patients taking placebo. Like all antiepileptic drugs, perampanel may increase suicidal ideation.

As data are limited, perampanel is not recommended in pregnancy. It is unknown if the drug is excreted in breast milk. The efficacy of progestogen-containing oral contraceptives may be reduced by the 12 mg dose of perampanel.

Although adjunctive treatment with perampanel reduces the frequency of partial seizures, only a minority of patients will get a significant reduction and few will become seizure free. In the pooled analysis the proportion of patients having at least a 50% reduction in seizures was 28.5% with 4 mg, 35.3% with 8 mg and 35% with 12 mg (see Table). In one study this responder rate was not significantly different from placebo, but there were unexplained geographical differences in these results.¹ The responder rates are better if the patient's other treatment does not include enzyme inducing drugs. In the absence of head-to-head studies, a systematic review found perampanel's efficacy, assessed by responder rates, was similar to lacosamide, retigabine and eslicarbazepine.⁵

T manufacturer provided the product information

REFERENCES *†A

1. French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. *Neurology* 2012;79:589-96.

2. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, Kumar D, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013;54:117-25.
3. Krauss GL, Serratos JM, Villanueva V, Endziniene M, Hong Z, French J, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012;78:1408-15.
4. Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. *Epilepsia* 2013;54:1481-9.
5. Khan N, Shah D, Tongbram V, Verdian L, Hawkins N. The efficacy and tolerability of perampanel and other recently approved anti-epileptic drugs for the treatment of refractory partial onset seizure: a systematic review and Bayesian network meta-analysis. *Curr Med Res Opin* 2013;29:1001-13.

First published online 19 December 2014

Simeprevir

Approved indication: hepatitis C

Olysio (Janssen-Cilag)

capsules containing 150 mg

Australian Medicines Handbook section 5.4

There are six main genotypes of hepatitis C, genotypes 1-6. In Australia, genotype 1 accounts for 50% of cases, genotype 3 for 30% and genotype 2 for 5%. Most people with chronic hepatitis C are treated with a combination of peginterferon and ribavirin. Sofosbuvir (Aust Prescr 2014;37:172-9), a recently approved nucleotide polymerase inhibitor, can be added to this. Also, the protease inhibitors boceprevir (Aust Prescr 2012;35:102-3) or telaprevir (Aust Prescr 2012;35:128-35) can be added for people with genotype 1 disease. Simeprevir is another protease inhibitor approved as an adjunctive treatment for genotype 1 (and genotype 4) disease. It works by inhibiting the viral protease NS3/4A, which is required for replication.

Simeprevir has been tested in several trials of previously untreated^{1,2} and treated^{3,4} people with genotype 1 infection. Patients were excluded from the

NEW DRUGS

trials if they had decompensated liver disease or liver disease unrelated to hepatitis C, or co-infection with another hepatitis C genotype, hepatitis B or HIV. The primary outcome was the proportion of patients who had achieved a sustained virologic response, defined as undetectable viral RNA 12 weeks after the end of treatment.

People who added simeprevir to peginterferon and ribavirin had significantly higher response rates compared to those who added placebo (see Table).¹⁻⁴ However, the presence of the naturally occurring viral NS3 Q80K polymorphism in people with genotype 1a infection was associated with lower response rates. For example in the QUEST-1 trial, the response rate to simeprevir was 52% (31/60) in people with the polymorphism compared to 85% (73/86) in those without it.¹ In an analysis of people who failed to respond to simeprevir or relapsed after treatment had finished, 92% (35/38) had one or more emerging amino acid substitutions in the viral protease.¹ Some of these mutations may also reduce the antiviral activity of telaprevir and boceprevir.

To assess long-term efficacy, 166 patients who had responded to simeprevir in the ASPIRE trial were followed up. After 16 months, all participants still had undetectable viral RNA.

The efficacy of simeprevir has also been tested in people co-infected with HIV and hepatitis C genotype 1 in an open-label, single-arm trial. HIV was well controlled in these patients. They received simeprevir 150 mg daily with peginterferon and ribavirin for 12 weeks followed by a period of continued peginterferon and ribavirin depending on their response. Twelve weeks after the end of treatment, 79% (42/53) of the treatment-naïve patients had responded compared to 87% (13/15) of those who had relapsed on previous treatment, 70% (7/10) of those who had partially responded and 57% (16/28) of those who had a null response to previous treatment.⁵

Another similarly designed open-label, single-arm trial assessed the simeprevir combination in 107 people with genotype 4 disease. Twelve weeks after the end of treatment, 83% (29/35) of treatment-naïve patients had undetectable viral RNA compared to 86% (19/22) of those who had previously relapsed, 60% (6/10) of those who had only partially responded to previous treatment and 40% (16/40) of those who had a null response to previous treatment. The study has not yet been published in full.

In a pooled safety analysis of placebo-controlled trials, discontinuation rates because of adverse events

Table Efficacy of daily simeprevir added to peginterferon and ribavirin in chronic hepatitis C genotype 1

Trial name and design	Treatment (duration)	Patient response [†]
QUEST-1 ¹ Randomised placebo-controlled phase III trial in treatment-naïve patients with genotype 1 disease	Simeprevir 150 mg (12 weeks) [§]	80% (210/264)
	Placebo (12 weeks) [#]	50% (65/130)
QUEST-2 ² Randomised placebo-controlled phase III trial in treatment-naïve patients [§]	Simeprevir 150 mg (12 weeks)	81% (209/257)
	Placebo (12 weeks)	50% (67/134)
PROMISE ³ Randomised placebo-controlled phase III trial in patients who had relapsed after previous treatment	Simeprevir 150 mg (12 weeks) [§]	79% (206/260)
	Placebo (12 weeks) [#]	36% (48/133)
ASPIRE ⁴ Placebo-controlled phase IIb trial in treatment-experienced patients [#]	Simeprevir 100 mg (12 weeks)	70% (46/66)
	Simeprevir 100 mg (24 weeks)	66% (43/65)
	Simeprevir 100 mg (48 weeks)	61% (40/66)
	Simeprevir 150 mg (12 weeks)	67% (44/66)
	Simeprevir 150 mg (24 weeks)	72% (49/68)
	Simeprevir 150 mg (48 weeks)	80% (52/65)
	Placebo (48 weeks)	23% (15/66)

[†] undetectable viral RNA (or less than 25 IU/mL) 12 weeks after the end of treatment in QUEST-1, QUEST-2 and PROMISE and 24 weeks after the end of treatment in ASPIRE

[§] peginterferon and ribavirin were continued for a further 12 or 36 weeks depending on response to treatment

[#] peginterferon and ribavirin were continued for a further 36 weeks regardless of patient response

were low for both simeprevir and placebo (2.2%). Pruritus (23.8% vs 17.4%), rash (22.9% vs 16.7%) and photosensitivity (4.7% vs 0.7%) were more common with simeprevir than with placebo.⁶ Patients should take appropriate precautions during sun exposure. Simeprevir should only be used in combination with peginterferon and ribavirin. This combination is contraindicated (pregnancy category X) in women who are pregnant or may become pregnant and men whose partners are pregnant. Adequate contraception must be used by men and women during treatment and for six months afterwards.

Simeprevir should be taken once daily with food for 12 weeks with peginterferon and ribavirin. Viral RNA concentrations should be monitored at 4 and 12 weeks. The duration of continuing peginterferon and ribavirin depends on the patient's viral RNA results and on their previous response to treatment (as detailed in the product information). Treatment should be stopped if a patient is not responding after four weeks.

Following a daily oral dose, maximum plasma concentrations are reached after 4–6 hours and steady state is reached after seven days. Simeprevir is metabolised in the liver and is predominately eliminated by biliary excretion. Renal excretion is negligible. Its terminal half-life is 41 hours in people with hepatitis C. Simeprevir exposure may be increased in people with moderate to severe liver impairment, although these people were not included in the trials. Drug exposure was increased in East Asian people, so monitoring for adverse effects is particularly important in this population.

Simeprevir is metabolised by cytochrome P450 (CYP) 3A4 so there is potential for many interactions with other drugs. Moderate–strong CYP3A4 inhibitors (e.g. erythromycin, ketoconazole, darunavir/ritonavir, milk thistle) are not recommended as they may increase the adverse effects of simeprevir, while inducers (e.g. carbamazepine, efavirenz, etravirine, rifampicin, St John's wort) may lead to loss of efficacy. Simeprevir may also increase exposure of concomitant drugs such as amiodarone, amlodipine, digoxin and statins. Monitoring is recommended and dose adjustment may be needed.

Adding simeprevir to peginterferon and ribavirin seems to produce a sustained virologic response in approximately 80% of people with hepatitis C genotype 1 or 4 disease. It was also effective in people co-infected with HIV, but has not been studied in those co-infected with hepatitis B. Simeprevir is less effective in people carrying the NS3 Q80K viral polymorphism. Treatment resistance can also develop and is associated with emerging mutations in the viral protease. It is not known if simeprevir

will be better than the other protease inhibitors, but patients may prefer its once-daily dosing compared to taking telaprevir or boceprevir three times a day. A preliminary study has shown promising efficacy of simeprevir given with sofosbuvir (with or without ribavirin) in an interferon-free regimen.⁷

 manufacturer did not supply data

REFERENCES *†

1. Jacobsen IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014;384:403-13.
2. Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014;384:414-26.
3. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a therapy 3 trial. *Gastroenterology* 2014;146:1669-79.
4. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014;146:430-41.
5. Dieterich D, Rockstroh JK, Orkin C, Gutierrez F, Klein MB, Reynes J, et al. Simeprevir (TMC435) with pegylated interferon/ribavirin in patients coinfecting with HCV genotype 1 and HIV-1: a phase 3 study. *Clin Infect Dis* 2014;59:1579-87.
6. Manns MP, Fried MW, Zeuzem S, Jacobson IM, Forns X, Poordad F, et al. Simeprevir with peginterferon/ribavirin for treatment of chronic hepatitis C virus genotype 1 infection: pooled safety analysis from phase IIb and III studies. *J Viral Hepat* 2014 Nov 3 [Epub ahead of print].
7. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet* 2014;384:1756-65.

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Umeclidinium bromide

Incruse Ellipta (GlaxoSmithKline)

62.5 microgram as dry powder for inhalation

Umeclidinium bromide with vilanterol

Anoro Ellipta (GlaxoSmithKline)

62.5 microgram/25 microgram as dry powder for inhalation

Approved indication: chronic obstructive pulmonary disease

Australian Medicines Handbook section 19.1

For more than a decade tiotropium bromide was the only long-acting anticholinergic bronchodilator available in Australia. In 2014 glycopyrronium bromide

NEW DRUGS

(Aust Prescr 2014;37:64-71), aclidinium bromide (Aust Prescr 2014;37:172-79) and umeclidinium bromide emerged.

Like the other members of its class, umeclidinium bromide is an antagonist at acetylcholine receptors. In the lungs this causes bronchodilation which begins within 15 minutes of an inhalation and lasts for over 24 hours. The bioavailability of an inhaled dose is about 13% with most of the absorbed dose being metabolised and then excreted in the faeces. Although this metabolism includes cytochrome P450 2D6 and umeclidinium is a substrate of P-glycoprotein, there are unlikely to be clinically significant pharmacokinetic drug interactions. No dose adjustments are needed in patients with renal or moderate liver impairment.

The recommended dose of 62.5 microgram once daily refers to the amount of umeclidinium, rather than umeclidinium bromide, in each blister on a foil strip. When the contents are inhaled through a specific device, a dose of 55 microgram umeclidinium is delivered.

A short-term trial compared umeclidinium with placebo in patients with chronic obstructive pulmonary disease (COPD) and a smoking history of at least 10 pack-years. At the start of the study the mean value of the forced expiratory volume in one second, before the next dose (trough FEV₁), was 1.21 L in the placebo group and 1.26 L in the umeclidinium 62.5 microgram group. After 12 weeks this had not risen in the 68 patients given placebo, but trough FEV₁ increased by 120 mL in the 69 patients who inhaled umeclidinium 62.5 microgram.

In a larger study, 418 patients inhaled umeclidinium 62.5 microgram and 280 inhaled placebo for 24 weeks. The mean trough FEV₁ was 1.2 L in both groups at the start of the study. It rose by 115 mL after 24 weeks of umeclidinium, but was unchanged in the placebo group. This study also included 421 patients who inhaled vilanterol 25 microgram (a long-acting beta₂ agonist) and 413 who inhaled a combination of umeclidinium 62.5 microgram and vilanterol 25 microgram. The combination increased trough FEV₁ by a further 52 mL compared with umeclidinium alone, and by 95 mL compared to vilanterol alone. All the active treatments reduced dyspnoea, and exacerbations were less frequent than with placebo (7-9% vs 13% of patients).¹

Common adverse events with umeclidinium were headache, cough and nasopharyngitis, but their frequency was similar in the placebo groups. The longer-term safety of a higher dose (125 microgram) was assessed in 227 patients. They were compared with 109 patients randomised to take a placebo. After 52 weeks adverse events which were more frequent than with placebo included supraventricular

tachycardia, sinus tachycardia and supraventricular extrasystoles. These arrhythmias are probably the result of antimuscarinic effects. Caution is therefore needed when prescribing umeclidinium for patients with arrhythmias and those at risk of narrow-angle glaucoma or urinary retention. There are no data about umeclidinium in pregnancy and lactation.

Umeclidinium is suitable as a maintenance treatment for chronic obstructive pulmonary disease and can be combined with a long-acting beta₂ agonist for more severe cases. However, there is little information about how this drug compares with similar treatments. One trial in the drug's development included patients who were randomised to take tiotropium 18 microgram once daily, but they were not compared with patients who took umeclidinium alone. Taking a combination of umeclidinium and vilanterol (62.5/25 microgram) for 24 weeks resulted in an average trough FEV₁ value that was 60 mL higher than with tiotropium alone.

Like other bronchodilators, not all patients will have a clinically significant response to umeclidinium. In the 24-week efficacy study only 53% of the patients inhaling umeclidinium had a clinically important difference in dyspnoea, while the response rate to placebo was 41%.¹

T manufacturer provided the product information for both products

REFERENCE [†]

1. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med* 2013;107:1538-46.

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

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

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

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



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